Effects of androgen deprivation therapy on cognitive functions in patients with metastatic prostate cancer: A multicentric, prospective study of the Society of Urological Surgery Andrology group

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Abstract

Abstract Aims of the study: The aim of this study was to investigate the impact of testosterone deficiency on cognitive functions in metastatic prostate cancer patients receiving androgen deprivation therapy (ADT). Methods: In this multicentric prospective study, 65 metastatic prostate cancer patients were evaluated. Demographic and clinical data were recorded. Cognitive functions were assessed using the Symbol Digit Modalities Test, the California Verbal Learning Test Second Edition, the Brief Visuospatial Memory Test - Revised, and the Trail Making Test. Depressive symptoms were assessed using the Beck Depression Inventory. Cognitive functions and depressive symptoms were recorded before the androgen deprivation therapy and at the 3- and 6-month follow ups. Results: At the basal cognitive assessment, the mean Symbol Digit Modalities Test, the California Verbal Learning Test Second Edition, the Brief Visuospatial Memory Test - Revised scores were 25.84 ± 17.54, 32.68 ± 10.60, and 17.63 ± 11.23, respectively, and the mean time for the Trail Making Test was 221.56 ± 92.44 s., and were similar at the 3-month, and 6-month controls ($p > 0.05$). The mean pretreatment, third and sixth month testosterone levels were 381.40 ± 157.53 ng/dL, 21.61 ± 9.09 ng/dL, and 12.25 ± 6.45 ng/dL ($p < 0.05$), and the total PSA levels were 46.46 ± 37.83 ng/mL, 1.41 ± 3.31 ng/mL, and 0.08 ± 0.14 ng/mL ($p < 0.05$), respectively. Conclusion: The ADT in patients with metastatic prostate cancer does not affect patients' cognitive functions and depressive symptoms. However, further prospective randomized studies with higher cohorts and longer follow up periods are needed.

Introduction

As of 2018, prostate cancer (PCa) was the second leading cause of cancer and the sixth common cause of cancer-related death in men [1]. Almost 20% of patients have locally advanced or metastatic disease at the time of first diagnosis [2]. The primary goal in the treatment of metastatic disease is to keep the se-

rum androgen level below the castration level of 50 ng/dL [3]. Medical castration with antiandrogen- or gonadotropin-releasing hormone (GnRH) agonists and surgical castration with bilateral orchiectomy are cornerstones of metastatic disease management [4]. However, lowering the serum testosterone below castration level may increase the risks of osteoporosis, anemia, gynecomastia, erectile dysfunction, and systemic disorders including diabetes and cardiovascular events [5,6].

Androgen deprivation affects cognitive functions in a majority of men over 65 years of age, whereas atherosclerotic or degenerative changes are more common. Although there are some relevant reports in the current literature [7], further comprehensive, prospective studies are needed to examine the effect of ADT on cognitive function. McGinty et al. conducted one of the largest and the most up-to-date systematic reviews, evaluating 14 studies (417 patients) and 7 cognitive domains and concluded that cognitive functions other than visuomotor ability remain largely unchanged [8]. Furthermore, Sun et al. conducted a meta-analysis of androgen deprivation therapy and concluded that it does not cause cognitive impairment [9]. However, due to the small number of prospective studies, the debate is still open regarding the impact of ADT on cognitive changes. Furthermore, greater age, advanced stage of primary disease, and presence of accompanying comorbidities may worsen underlying cognitive disorders in patients under long-term ADT.

The present study aimed to evaluate changes in cognitive functions and depressive symptoms in men who received ADT for metastatic prostate cancer using GnRH analogues.

Patients and Method

This prospective, multicentric study was carried out in accordance with the declaration of Helsinki after approval of the Ethics Committee of Zonguldak Bulent Ecevit University (Date: 18/03/2020; Approval Number: 2020/06). All participants were informed in detail about the design of the study, and their consent was obtained. For a power analysis, a total of 48 consecutive men diagnosed with metastatic prostate cancer and receiving GnRH analogues for ADT were enrolled the study. Cognitive domains including verbal memory, visual-spatial memory, information processing speed, and executive functions were evaluated at the third and sixth month of ADT to discover any change. Patients who had previously been diagnosed with dementia or psychiatric disease and who were receiving antidepressant or antipsychotic therapy were excluded. Patients consuming alcohol or drugs, with a history of systemic chemotherapy, with central nervous system metastases, with inadequate vision or hearing impairment that could interfere with neurocognitive tests and previous brain damage, or who had had brain injury or brain surgery that could affect cognitive functions were excluded from the study.

According to the ADT protocol, total prostate-specific antigen (PSA) and testosterone levels were measured prior to ADT from a fasting morning venous blood sample using the enzyme-linked immunosorbent assay method. Patients were given antiandrogen (50 mg bicalutamide per day) for at least 10 days, then continued with subcutaneous administration of 22.5 mg leuprolide quarterly.

Neuropsychological tests

All the neuropsychological assessments were performed prior to ADT and at the third and sixth months of ADT. Four neuropsychological tests, including the Symbol Digit Modalities Test (SDMT) [10], the California Verbal Learning Test, second edition (CVLT-II) [11]; the Brief Visuospatial Memory Test - Revised (BVMT-R) [11]; and the Trail Making Test (TMT) [12,13]were performed to cover 4 main cognitive areas. Depressive symptoms were measured using the Beck Depression Inventory (BDI) [14]. All the neuropsychological tests were completed in approximately 15–20 min in the supervision of trained physicians.

Attention and speed of processing : A written version of the SDMT was used to assess visual spatial scanning, attention and concentration, and information processing speed. Patients were asked to match as many symbols with digits 1–9 as possible in 90 s. The SDMT takes approximately 5 min to complete. The test result represents the number of correct answers [10].

Verbal memory : The CVLT-II is the standard scale of verbal learning and memory in clinical neuropsychology and has been widely used in clinical trials. The CVLT-II is composed of a 16-item word list. The

examiner reads out the list of words to the participant in the same order. After each reading, the patient repeats as many words as possible in any order. The learning score represents the total number of correct words remembered in the first 5 attempts [11].

Visuospatial learning and memory : BVMT-R is a measurement tool of visuospatial learning and memory; it consists of 3 recall attempts. At the learning attempts, patients were asked to view 6 geometric figures for 10 s. Then they were asked to draw as many symbols as they can remember, in the correct position on an empty page. These drawn symbols are scored from 0 to 2, depending on accuracy and location, for a maximum of 12 points for each attempt to recall and draw the 6 figures. The highest possible score is 36 total for 3 recall attempts [11].

Executive functions: Executive functions comprise working memory, complex attention, problem solving, and response inhibition. The TMT evaluates visual search, attention, and executive function and is divided into 2 parts. The first part of the test evaluates speed and psychomotor attention and requires consecutively connecting randomly-distributed, encircled numbers from 1 to 25 [12]. The second part requires the subject to connect numbers and letters in alternating, ascending order [13]. Patients were asked to finish the test as quickly as possible, and the test time was recorded. A standardization study of this test in Turkish adults over the age of 50 was conducted by Cangöz et al [15].

Depressive symptoms : The BDI is used to assess depressive symptoms. In this scale, patients were asked to mark the most accurate expressions describing how they felt in the week leading up to and including the day of the test. The BDI test consists of 21 questions, with the following possible responses: not at all (0); mild (1); moderate (2), and severe (3). According to the scoring system, a 0–10 score is considered normal, 11–16 is mild mood disturbance, 17–20 is borderline mood, 21–30 is moderate depression, 31–40 is severe depression, and [?]41 is extreme depression [14].

Statistical Analysis

All statistical results were analyzed using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows. Mean and median values, standard deviation, and frequency values were calculated for the descriptive statistical data. A chi-squared test was used to compare ratios in categorical variables. Due to the low number of participants, the Shapiro–Wilk normality test was used to determine whether the study data were normally distributed. The Friedman test was used for the data that did not show normal distribution, and an evaluation of normally-distributed data was made by repeated measurement analysis. A Spearman's rank correlation test was used for the data that was not normally distributed, and the relationship among the normally-distributed data was evaluated using a Pearson correlation analysis. A p value of $<.05$ was considered statistically significant.

Results

Of the 65 participants, 8 were excluded from the cognitive component of the study due to low scores on the Mini-Mental State Exam, and 9 with incomplete data were excluded. Results of the remaining 48 patients were analyzed.

The mean age of the patients was 69.08 +- 4.77 years, and the mean body mass index was 25.73 +- 2.93 kg/m^2. Demographic characteristics of the patients are shown in Table 1. The mean pretreatment, third month, and sixth month total PSA levels were 46.46 +- 37.83 ng/mL, 1.41 +- 3.31 ng/mL, and 0.08 +- 0.14 ng/mL, respectively. The mean testosterone level significantly decreased in the 3- (21.61 +- 9.09 ng/dL) and 6-month controls (12.25 +- 6.45 ng/dL) from the pretreatment level (381.40 +- 157.53 ng/dL) ($p = 0.001$) (Table 2). The transrectal ultrasound guided prostate biopsy Gleason scores of the patients are shown in Figure 1.

The mean baseline, 3-month and 6-month SDMT scores were 25.84 +- 17.54, 23.30 +- 17.40 and 23.23 +- 16.03, respectively ($p = 0.092$). The mean pretreatment, 3-month, and 6-month CVLT-II scores were 32.68 +- 10.60, 31.56 +- 10.73, 29.43 +- 11.30, respectively ($p= 0.297$). The mean baseline, 3-month, and 6-month BVMT-R scores were 17.63 +- 11.23, 16.57 +- 11.13, and 16.12 +- 10.21, respectively ($p = 0.731$). The

mean baseline, 3-month, and 6-month time for the TMT was 221.56 +- 92.44 s, 225.78 +- 87.47 s and 244.68 +- 77.37 s, respectively (p = 0.731) (Table 3). The mean baseline, 3-month, and 6-month BDI scores were 11.15 +- 6.40, 11.78 +- 5.45 and 12.00 +- 10.58, respectively (p = 0.61).

Discussion

Androgen deprivation therapy is commonly used in the treatment of locally advanced disease with combination therapies and in metastatic prostatic cancer patients. Androgen suppressing treatments cause side effects such as anemia, flushing, fatigue, gynecomastia, osteoporosis, erectile dysfunction, diabetes, and cardiovascular complications. The present study was designed to evaluate the effect of ADT on cognitive functions in metastatic prostate cancer patients. The study used 4 cognitive tests to interpret 4 main cognitive domains: information processing speed, verbal memory, visuospatial memory, and executive functions. In a large, prospective study about cognitive functions in prostate cancer patients, it has been shown that ADT has no significant effect on cognitive function [16]. However, some studies have demonstrated that patients show greater impairment after ADT in visuomotor functions, visuospatial abilities, and executive functions as compared to healthy patients [8,17]. Furthermore, studies have shown that higher free testosterone levels are positively associated with visuospatial function, visual memory, visuomotor scanning, and episodic memory [18]. Some systematic reviews and meta-analyses have been conducted regarding ADT and cognition in prostate cancer patients [8,17,19]. Nelson et al. show that patients who receive ADT have a deterioration in 1 or more cognitive areas (usually visuospatial skills or executive functions), at rates of 47–69%. Jamadar et al. conclude that spatial memory in particular may be sensitive to ADT. The largest and most up-to-date systematic review, conducted by McGinty et al., evaluates 14 studies (417 patients) and 7 cognitive domains. This review concludes that cognitive functions other than visual skills remain largely unchanged.

Although Gonzalez et al. have reported a significant risk of cognitive impairment with ADT, in a prospective, controlled study conducted by Alibhai et al. in 2010, cognitive impairment is not shown in elderly men with prostate cancer after 12 months of ADT [16,20]. However, one finding of the regression analysis is that the use of ADT is associated with worse immediate memory, working memory, and visuospatial ability, although this is not confirmed by other analytical approaches. Alibhai et al. have followed one patient group for 36 months to evaluate the long-term results, again showing that there is no relationship between the use of ADT and cognitive impairment [21].

Preclinical studies have shown that ADT can increase the risk of dementia or Alzheimer's disease through various mechanisms, such as beta-amyloid accumulation in the central nervous system [22,23]. Androgens have also been associated with neuron growth and axonal regeneration, and low testosterone levels and ADT have been shown to increase the risk of cardiovascular and metabolic diseases [6]. Anatomical studies have shown the wide distribution of androgen receptors in areas related to memory, emotional processing, and libido, mainly in the hippocampus and amygdala. Neurological changes associated with androgen deprivation occur in the same regions affected by the age-related decline and are consistent with our knowledge of the loci of androgen receptor expression [24]. In the population of elderly males without prostate cancer, low levels of free testosterone have been associated with decreased visuospatial memory and abilities, as well as verbal memory and processing speed [25].

Marzouk et al. have investigated the relationship between 12-month ADT and cognitive changes using the functional assessment of cancer therapy - cognitive function (FACT-Cog) assessment tool [7]. However, data from patient-reported outcome (PRO) measurements should be carefully evaluated, as PROs have not been validated as a tool to assess cognition. This is because they are subjective, based on a personal perception of cognitive function, and can be influenced by factors such as mood and fatigue. Objective tests remain the gold standard for measuring cognitive function, as they allow the identification of treatment-related cognitive problems that can affect daily life. However, it should be kept in mind that PROs provide a useful measure of the effect of cognitive functions on the perception and quality of life of the patient; thus, PROs should also be used in studies [26].

In a population-based analysis, 101,089 men (15,748 with PCa receiving ADT, 34,865 with PCa not treated

with ADT, and 50,476 without cancer) were evaluated using Medicare data linked to surveillance, epidemiology, and end results data to assess exposure to ADT. The cognition of PCa patients not treated with ADT and men with PCa treated with ADT were compared. In that study, ADT was shown not to be associated with an increased risk of cognitive impairment (hazard ratio 0.99; 95% CI 0.94–1.04) [27]. The present study included 48 patients with metastatic prostate cancer scheduled to undergo ADT and followed them for 6 months, testing 4 main cognitive domains: visuospatial memory, executive functions, information processing speed, and verbal memory. To test cognitive functions, the SDMT, CVLT, TMT, and BVMT-R tests were chosen due to their availablility in Turkish, easy application in daily practice, and ability to measure cognitive functions in a short time frame (i.e., 15 min to conduct all 4 tests). In some studies examining cognitive functions in men who underwent ADT using objective cognitive assessment tools, impairment in verbal memory, spatial abilities, and attention has been shown [28,29]. However, in other studies, no significant change in cognition is observed with ADT, consistent with our study [21,30].

Some methodological differences exist among previous studies, such as intermittent versus continuous ADT, various methods of creating androgen deprivation (i.e., orchiectomy, gonadotropin-releasing hormone agonists, and other treatments), varied timing of cognitive evaluation visits, the presence of concurrent treatments, and the characteristics of the control groups [8,17,19]. Furthermore, some meta-analyses report that the relationship between ADT and cognitive impairment is not reliably confirmed [8,9].

The neuropsychological tests used in the studies in which all cognitive areas are evaluated take about 60 min. This time period is not practicable in daily practice; thus, it is important to evaluate the cognitive states of patients globally in a shorter time. By contrast, the cognitive assessment tests used in this prospective study were short (15 min.) and easy for both the patient and the physician, the reasoning being that they are more viable for daily practice. Developing standardized tools for assessing cognitive impairment and making them applicable in daily practice is thought to be important for comprehensive monitoring of patients.

Conclusion

In conclusion, ADT has not affected 4 main cognitive domains including; visuospatial memory, executive functions, information processing speed, and verbal memory. Due to a lack of data, the debate is still open regarding the impact of ADT on cognitive changes. Further prospective studies are needed to clarify the impact of ADT on cognitive functions with longer follow-up periods.

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Figure Legends

Table 1: Demographic characteristics of the participants. +standard deviation; ++hypertension; SScoronary artery disease; Pdiabetes mellitus; ᵅchronic renal failure

Table 2: Testosterone levels and PSA levels during follow up. +Standard deviation. Comparison of mean PSA levels was done by Friedman analysis, while the change in testosterone levels was evaluated by repeated measurement analysis. *Comparison of the baseline value with the averages in the third month.

**Comparison of the baseline value with the averages in the sixth month. ***Comparison of the averages in the third and sixth months.

Table 3: Comparison of the cognitive tests of the study group at baseline, 3rd month of ADT, and 6th month of ADT. Comparison of mean BVMT-R scores and TMT times were evaluated by Friedman analysis, the change in SDMT scores and CVLT scores were evaluated by repeated measurement analysis. +Standard deviation

Figure 1: Prostate biopsy Gleason scores of the participants

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