The Association of A Number of Risk Factors With Depression in Patients With Prostate Cancer Undergoing Androgen Deprivation Therapy

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Purpose: To identify factors affecting depressive symptoms in patients undergoing androgen-deprivation therapy (ADT) to treat prostate cancer.

Materials and Methods: The patients with prostate cancer visiting the psychiatry department without referral because of depressive symptoms while undergoing ADT participated. To assess depressive symptoms, the Beck Depression Inventory (BDI) was used. To identify the risk factors affecting depressive symptoms, univariate regression and multiple linear regression analyses were implemented.

Results: The mean (± SD) age, age when initiating ADT, duration of ADT, serum testosterone level and BDI scores of participants (n = 45) were 73.9 ± 7.9 years, 72 ± 8.5 years, 33 ± 31.6 months, 214.9 ± 219.5 ng/dL and 18 ± 13.5 points. The androgen dependent and independent were 26 and 9 patients. Eight of these androgen-independent patients underwent concurrent chemotherapy. Twenty-one patients were treated with bicalutamide and 24 with leuprolide. Of the clinical variables affecting BDI scores, the type of ADT drug ($P < 0.001$), serum testosterone level ($P = 0.003$), and age at diagnosis ($P < 0.001$) were significant.

Conclusion: Efforts to diagnose and treat depression appropriately, especially if depressive symptoms change in patients undergoing ADT to treat prostate cancer who are using an LHRH agonist (leuprolide), have low testosterone level, or are older at the age when initiating ADT.

Keywords: Androgen-deprivation therapy; Depression; Prostate cancer; Quality of life.

INTRODUCTION

Prostate cancer is one of the most common cancers among men, with approximately 240,000 men being newly diagnosed with prostate cancer in the US[1]. Androgen-deprivation therapy (ADT) has been historically used only in advanced stage cases, but has been increasingly selected as a treatment method in patients with asymptomatic metastasis, node-positive status, and elevation of prostate specific antigen (PSA) after treatment[2-4].

The known side effects of ADT include loss of libido, gynecomastia, erectile dysfunction, anemia, cardiovascular disease, osteoporosis, and depression[5]. Specifically, depression has been shown to have an association with ADT[6,7]. Depressive symptoms in patients with cancer are closely associated with a variety of complications, ranging from cancer recurrence to decreased compliance with treatment[8]. Nevertheless, oncologists do not readily recognize psychiatric problems like depression and, subsequently, patients requiring psychiatric treatment are not properly managed[9,10]. Recently, the quality of life of patients has become particularly important as the survival of prostate cancer patients undergoing ADT has increased and depressive symptoms greatly influence quality of life. However, there have been few studies that have investigated the factors affecting depressive symptoms in prostate cancer patients undergoing ADT.

The present study aimed to identifying factors affecting depressive symptoms occurring in patients undergoing ADT, as the number of patients treated with ADT increases, to promote an increase in quality of life through proper management and diagnosis.

MATERIALS AND METHODS

Demographic and Clinical characteristics

The inclusion criteria of this study were as follows. Patients with prostate cancer histologically confirmed at Gachon University Gil Medical Center between May 2005 and June 2016 who visited the Psychiatry Department without consultation of the oncology staff due to depressive symptoms while receiving ADT. All participants had an elementary school education or higher, and were married.

Patients with the following exclusion criteria were excluded: Prior to ADT, the patients had a history of psychiatric disorders, including depression, neurological disorder involving the brain, or hypogonadism, they were diagnosed with or treated for cancer beyond prostate cancer, or they used male hormones for cancer treatment purposes.

Depending on the ADT schedule, the patients received an LHRH agonist (leuprolide depot 11.25 mg) intramuscularly every 12 weeks or an anti-androgen agent

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Table 1. Characteristics of patients undergoing ADT

Characteristic[a]	Value
Mean age (years)	73.9 ± 7.9
Mean age at diagnosis (years)	72 ± 8.5
Period of ADT (months)	33 ± 31.6
Type of ADT drug (bicalutamide or leuprolide)	21/24 (47/53)
Androgen dependence (androgen-dependent or androgen-independent)	36/9 (80/20)
Disease response to current treatment (responder/ stable disease or progressive disease)	36/9 (80/20)
Treatment with concurrent chemotherapy (yes or no)	8/37 (82/18)
Serum testosterone (ng/dL)	214.9 ± 219.5
Beck Depression Inventory (score)	18 ± 13.5

Abbreviations: ADT: androgen deprivation therapy; BDI: Beck Depression Inventory
[a]Values are presented as the mean (± SD) or number (%).

(bicalutamide 150 mg) orally daily. Those treated with leuprolide also took bicalutamide 50 mg for a month to prevent disease flare-ups that may occur during the initial leuprolide administration.

This study was approved by the Institutional Review Board (IRB No. GCIRB 2014-274) of our institution.

Measures of depressive symptomatology

The Beck Depression Inventory (BDI) is a 21-item self-report used to evaluate the severity of depressive symptoms, to screen for depression, and to assess the severity of depressive symptoms, even in cases with symptomatology overlap with neurovegetative symptoms[11]. The total score range from 0 to 63, with higher scores indicating more severe depressive symptoms. The BDI is a reliable tool to measure the severity of depressive symptoms. Lee et al. showed that the Cronbach's alpha for BDI total score was 0.89 and the correlation between the BDI and the patient health questionnaire-9 was strong (r = 0.75)[12]. Participants completed the BDI with the aid of a trained psychiatric nurse.

Variables affecting depressive symptoms

Univariate regression analysis was performed to identify the factors affecting depressive symptoms at the BDI score in patients undergoing ADT after diagnosis of prostate cancer, current age, age when initiating ADT, type and length of ADT, disease response to ADT, androgen dependence, serum testosterone level and use of concurrent chemotherapy with ADT. Generally, a step wise multiple linear regression analysis was then performed with backward elimination to select an appropriate model, and a p value > 0.20 was used for removal. However, we analyzed for all variables by the multivariate regression analysis. Because the number of variables affecting depressive symptoms occurring in patients undergoing ADT was relatively small, (only eight variables, in this study).

Disease response status (responder/stable disease or progressive) was determined per the recommendation of the Prostate Specific Antigen (PSA) Working Group. Patients stable or responding to ADT were defined as androgen-dependent and those in whom prostate cancer progressed despite ADT treatment were defined as androgen-independent[13]. There have been some studies of the relationship between testosterone level and depressive symptoms in prostate cancer patients. Barrett Connor et al. found that the BDI score was significantly and inversely associated with testosterone ($P < 0.007$) independent of weight change and physical activity in prostate cancer patients[14,15].

Table 2. Association of BDI scores with clinical variables by univariate analyses.

Variables	β ± SE	*P*-value
Current age	0.261 ± 0.203	0.204
Type of ADT drug	4.696 ± 3.158	0.144
Length of ADT	-0.102 ± 0.049	0.044
Age when initiating ADT	0.334 ± 0.184	0.078
Serum testosterone	-0.007 ± 0.007	0.342
Disease response to ADT	7.306 ± 3.882	0.067
Androgen dependence	7.306 ± 3.882	0.067
Concurrent chemotherapy	-6.811 ± 4.096	0.104

Abbreviations: ADT, androgen deprivation therapy; SE, standard errors

RESULTS

Forty-five patients with prostate cancer visiting the psychiatry department without referral because of depressive symptoms while undergoing ADT participated in this study. The mean (± SD) age of participants was 73.9 ± 7.9 years and the mean age at diagnosis was 72 ± 8.5 years. The mean duration of ADT treatment was 33 ± 31.6 months. Twenty-one patients were treated with bicalutamide and 24 with leuprolide. Thirty-six patients were defined as being androgen-dependent and 9 as being androgen-independent. Eight of these androgen-independent patients underwent concurrent chemotherapy. The mean serum testosterone level was 214.9 ± 219.5 ng/dL among all participants. The mean BDI score across all participants was 18 ± 13.5 points, respectively (**Table 1**).

The results of the univariate regression analysis were shown in **Table 2**. However, we analyzed for all clinical variables (current age, age when initiating ADT, type and length of ADT, disease response to ADT, androgen dependence, serum testosterone level, use of concurrent chemotherapy with ADT) with the BDI score by the multivariate regression analysis, because of the relatively small number of variables. The results showed that among the tested variables, the type of ADT drug ($P < 0.001$), serum testosterone ($P = 0.003$), and age at initiating ADT ($P < 0.001$) were statistically significant (**Table 3**).

DISCUSSION

This study was conducted to investigate the conditions affecting depressive symptoms occurring during treatment with ADT. The severity of depressive symptoms was measured with the BDI, and indicated that depression is likely to be severe in patients undergoing ADT to treat prostate cancer who are using an LHRH agonist

Table 3. Association of BDI scores with clinical variables by multiple linear regression analyses.

Variables	Parameters β ± SE	Partial R^2	P-value
Type of ADT drug	51.537 ± 11.818	0.178	< 0.001
Serum testosterone	0.087 ± 0.027	0.134	0.003
Age when initiating ADT	0.757 ± 0.160	0.154	< 0.001

Abbreviations: ADT, androgen deprivation therapySE, standard errors

(leuprolide), have low testosterone level, or are older at the age of initiating ADT.

In prostate cancer treatment, LHRH agonists are commonly used to substantially decrease levels of serum testosterone, and anti-androgen agents are commonly used because they act on androgen receptors. LHRH agonists generate a biphasic response by initially causing elevation of luteinizing hormone and follicle-stimulating hormone levels, followed by downregulation of the release of gonadotropin-releasing hormone in the hypothalamus and gonadotropins in the anterior pituitary gland, which subsequently give rise to the inhibition of androgen synthesis in the testes[16]. On the other hand, anti-androgen agents compete with androgens for binding to the androgen receptor, suppressing the effects of androgen in prostate cancer cells. Therefore, anti-androgen agents do not cause decreases in the serum testosterone level[17]. The effect of ADT on depressive symptoms has yet to be elucidated. The studies have reported that ADT affects depression for other reasons, such as through the involvement of neurochemicals such as serotonin[18]. Another study indicated that ADT worsens depressive symptoms by affecting pro-inflammatory cytokines such as IL-1 and IL-6[19]. We believe that a low testosterone level is related to depression, as testosterone reduction leads to a worsening of depressive symptoms, even in healthy men[20]. Additionally, a study that compared a group undergoing treatment with ADT for prostate cancer with several control groups showed that depressive symptoms increased as testosterone level decreased in the ADT group[21,22]. We found that the testosterone reduction was significantly correlated with a worsening of depressive symptoms in the patients treated with leuprolide, an LHRH agonist.

It has been reported that various psychiatric disorders in the elderly (elderly patients) are not properly recognized. Furthermore, they are not properly identified due to the presence of other physical symptoms[23]. Therefore, if depressive symptoms worsen in elderly patients undergoing ADT, their quality of life will likely be negatively affected. However, because of difficulties in diagnosis, it is important to pre-screen elderly patients undergoing ADT in whom depression is at high risk of worsening, and to diagnose and treat appropriately. The elderly with depression have a few characteristics.

Table 4. Recommendations to minimize the risk of depression in patients undergoing ADT

1	The patient's disease history and a detailed physical examination before initiating treatment with ADT
2	Administering a self-reporting questionnaire
3	Referred to psychiatry department for proper treatment

Abbreviations: ADT: androgen deprivation therapy

In many cases, depression is accompanied with medical comorbidities, impaired sleep quality, and cognitive impairment, responsiveness to initial treatment of depression is low due to a spouse's death or reduced psychosocial resources, and it is difficult to treat for a sufficient period[24,25]. Accordingly, the elderly who experience depression for the first time require a long treatment period to achieve remission and have a higher recurrence rate (7% vs. 15%); thus, the prognosis is unfavorable[26,27]. Particularly, in patients over age 70 who experience depression for the first time, it very frequently recurs with concurrent cognitive impairment, and the suicide rate is very high. Thus, they should be diagnosed and treated with accuracy[28]. In the present study, the results of the analysis conducted to identify factors affecting depressive symptoms of patients undergoing ADT showed that the older the patients are at age initiating ADT, the more severe the depressive symptoms ($P < 0.001$).

Therefore, medical staff who administer ADT should always be aware that the likelihood of patients with risk factors for developing depression is high and prompt and appropriate diagnosis and treatment when depression occurs is paramount to prevent a decrease in their quality of life. Hence, we have the following recommendations for the medical staff treating patients with risk factors for depression (**Table 4**).

First, before initiating treatment with ADT, the patient's disease history should be ascertained and a detailed physical examination should explore the history of depression and identify co-occurring illnesses. As mentioned, it is often difficult to diagnose depression in cancer patients or elderly patients because of the presence of comorbidities[29]. Therefore, medical staff should try to recognize worsening of depressive symptoms during treatment with ADT by thoroughly understanding the comorbidities or physical abnormalities of the patients.

Second, changes in depressive symptoms in patients with risk factors should be followed up while receiving ADT, by for example, administering a self-reporting questionnaire. In a study that studied patients undergoing ADT, depressive symptoms increased after ADT was administered and around the time when testosterone level precipitously dropped[21]. If it is difficult to confirm depressive symptoms, the patient can be referred to a psychiatrist with the recommendation that they visit the department for screening on a regular basis.

Third, if depressive symptoms worsen in a patient with risk factors, they should be diagnosed and treated by psychiatrists. With an increase in the elderly population, diverse treatment approaches have been introduced to treat depression in the elderly who experience the disorder for the first time. Recently, many treatment approaches appropriate for elderly patients have been introduced and we believe that an appropriate diagnosis can improve treatment outcomes[30].

This study had some limitations. As the study participants were patients who voluntarily visited a psychiatrist due to changes in depressive symptoms while undergoing ADT, the sample size was small. Based on the current findings, a study investigating factors affecting changes in depressive symptoms in patients undergoing ADT is underway. As a follow-up study, we are planning to present an approach to help patients undergoing ADT lead a healthier life, physically and mentally, by

complementing the limitations of the present study.

CONCLUSIONS

We believe that efforts should be taken to diagnose and treat depression appropriately, especially if depressive symptoms change in patients undergoing ADT to treat prostate cancer who are using an LHRH agonist (leuprolide), have low testosterone level, or are older at the age of initiating ADT.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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