Psychological distress in men with prostate cancer receiving adjuvant androgen-deprivation therapy

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Abstract

Objectives: To compare the occurrence of depression, anxiety, self body image perception, sleep disturbances, and diminished quality of life in prostate cancer patients undergoing adjuvant androgen-deprivation therapy (ADT) as opposed to patients in follow-up alone.

Methods and materials: Hospital Anxiety and Depression Scale, Pittsburgh Sleep Quality Index, Restless Legs Syndrome Study Group essential diagnostic criteria, Body Image Scale and Functional Assessment of Cancer Therapy Prostate were administered to consecutive prostate cancer patients who underwent radical prostatectomy or radiation therapy and are presently either under adjuvant ADT or included in a follow-up program.

Results: Of the 103 patients enrolled, 49 (47.6%) were receiving adjuvant ADT and 54 (52.4%) were not. Compared with the controls, the patients undergoing ADT showed higher levels of depression (P= 0.002), worse self body image perception (P = 0.001), worse quality of life (P = 0.0001) and worse sleep quality (P = 0.04). ADT was significantly associated with depression at multivariate analysis after adjustment for age, stage, Gleason score, as well as demographic and social variables (P=_ 0.001). Depression scores showed a strong inverse correlation with quality of life scores (P = 0.01).

Conclusions: Adjuvant ADT is associated with depression, worse quality of life, and altered self body image in prostate cancer patients.

1. Introduction

Androgen-deprivation therapy (ADT) is the mainstay of treatment for prostate cancer patients with metastatic disease [1]. In prospective randomized clinical trials, ADT was found to be effective in reducing the risk of recurrence in high-risk men undergoing radical prostatectomy [2] and in improving overall survival in high-risk men after radiation therapy [3]. Although increasingly prescribed in apparently healthy men with a long life expectancy, the potential benefits of ADT still need to be carefully weighed against the risks of long-term toxicity.

Several studies have shown that ADT has long-term side effects, including cardiovascular diseases, diabetes, anemia, bone fractures, obesity, metabolic syndrome, and decreased lean body-mass [4], all of which can diminish quality of life [5–7]. Furthermore, ADT can also have neuropsychiatric effects including depression.

Low testosterone levels may, in fact, alter serotonin neurotransmission [8], negatively affecting mood as demonstrated in animal models [9]. Also, testosterone deficiency may decrease cerebral perfusion in the brain regions involved in memory, reasoning, judgment, and emotions [10], leading to a deterioration in mental and overall wellbeing [11,12]. Studies in elderly subjects and non-cancer patients have reported a clear association between testosterone levels and depressive symptoms [13]: lower testosterone levels in older men have been associated with more depressive symptoms [14,15], which seem to disappear with testosterone hormone treatment [16,17]. Besides contributing to the onset of depressive disorders, decreased testosterone blood levels can cause breast tenderness and loss of penile length or volume. These changes, together with unwanted weight gain, lead to a worsening of self body image perception [18].

Low circulating testosterone levels are associated with diminished sleep efficiency and fewer rapid eye movement (REM) sleep episodes with altered REM sleep latency [19]. In a large study on prostate cancer patients treated with radical prostatectomy, androgen blockade-related symptoms were associated with a significantly higher likelihood of insomnia syndrome [20]. As insomnia and worsened body image perception are both notoriously linked to depression [21–24], they can concur in the development of depressive symptoms associated with low testosterone levels.

These premises notwithstanding, study results on depression in prostate cancer patients undergoing ADT remain controversial: one pilot study found major depressive disorder in a high percent of prostate cancer patients under ADT [25], whereas a large population-based analysis of depressive and cognitive symptoms in patients with prostate cancer

failed to show a higher prevalence of depressive symptoms in ADT treated patients vs. non-treated patients after adjusting for age, comorbidities, and disease stage [26].
The present study was designed to investigate the frequency of depression and other contributory physical and psychological distresses, such as quality of life deterioration, worsening of self body image perception, and sleep disorders, in a group of consecutive prostate cancer patients referred for ADT as adjuvant therapy after loco-regional treatment as compared with a group of prostate cancer patients referred for follow up only.

2. Material and methods

2.1. Subjects

From March to May 2007, consecutive patients either under adjuvant ADT or included in a follow-up program after loco-regional treatment of localized prostate cancer were recruited at the Prostate Cancer Unit, San Luigi Hospital, Orbassano, Italy.
Eligibility criteria were: (1) histologically confirmed diagnosis of prostate cancer; (2) previous loco-regional treatment of primary tumor (prostatectomy or 3D conformational radiotherapy); (3) absence of metastatic disease; (4) at least 6 months follow-up after primary treatments; (5) ability to do physical and psychological tests; (6) absence of major comorbidities; (7) performance status 0 or 1 (Eastern Cooperative Oncology Group [ECOG] scale); (8) written informed consent. To be included in the study, ADT-treated patients had to have serum testosterone levels _ 0.5 ng/ml.
Exclusion criteria were: (1) a past history of neuropsychiatric disease or consumption of anxiolytics, antidepressants, or other psychotropic drugs before the diagnosis of prostate cancer; (2) progressive disease, defined as an increase in serum prostate-specific antigen (PSA) levels at 2 consecutive assessments and/or new lesions in bone, viscera, or lymph nodes detected at study entry. The study protocol was approved by the local Ethical Committee, and written informed consent was obtained from all patients before entry into the study.
The patients were divided into 2 groups according to whether they received adjuvant hormone treatment or not. Patients with low or intermediate risk according to National Comprehensive Cancer Network (NCCN) guidelines criteria [27] who had undergone radical prostatectomy were referred for follow-up alone. Adjuvant hormone therapy was recommended to all patients who had received radiation therapy and to high-risk patients undergoing radical prostatectomy.
ADT consisted of 11.25 mg LHRH-A alone, given subcutaneously or intramuscularly every 3 months. Antiandrogens (bicalutamide or flutamide) were added to the LHRH-A regimen during the first month of therapy to prevent tumor flare.

2.2. Assessment instruments

In order to integrate both clinical and psychological assessment at the onco-urologic follow-up visit, the data were collected using question-based interviews conducted by 2 research assistants, 1 from the nursing staff and the other from the clinical psychology group. The first section of the 2-part questionnaire was composed of general questions about gender, age, education level, civil status, place of residence (i.e., urban, suburban, rural), and time since the start of anticancer therapy.
The second section consisted of: Functional Assessment of Cancer Therapy-Prostate (FACT-P): a multidimensional, self-report instrument for quality of live (QoL) assessment, specifically designed for use with prostate cancer patients. It consists of 27 core items that assess patient function in four domains: physical, social/ family, emotional, and functional well-being; it is further supplemented by 12 site-specific items that assess for prostate-related symptoms (Prostate Cancer Scale). Each item is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as a global QoL score. Higher scores reflect better QoL [28]. Internal consistency as measured by Cronbach's _ was at least 0.84 for all 5 subscales. Hospital Anxiety and Depression Scale (HADS): this tool measures levels of anxiety and depression and investigates for the presence of mood disorder in hospital populations and hospital outpatients [29]. It consists of 2 subscales that measure anxiety and depression status separately. Each subscale contains 7 items, rated on a 4-point (0 –3) scale, which are then added to produce a score from 0 to 21 for both anxiety and depression. For each subscale, a score of 0 to 7 indicates a normal condition; 8 to 10 is suggestive of anxiety or depression; 11 or higher indicates the probable presence of mood disorder. Internal consistency as measured by Cronbach's _ was 0.78 and 0.73, respectively.
Body Image Scale (BIS): this 10-item assessment instrument designed for use with cancer patients [30] measures the impact of medical and surgical treatments on self-consciousness, physical and sexual attractiveness, masculinity, satisfaction with body and scars, body integrity, and avoidance behavior. Each of the 10 BIS items are scored from 0 (not at all), through 1 (a little), 2 (moderately), to 3 (very much), giving a summary score range of 0–30. Higher scores denote increased negative change or dissatisfaction with body image. The BIS was employed to evaluate the impact of hormone therapy on self body perception. Internal consistency as measured by Cronbach's _ was 0.77.
Pittsburgh Sleep Quality Index (PSQI): this tool measures subjective sleep quality in the preceding 1-month period and consists of 19 self-rated questions and 5 questions rated by a bedpartner or roommate. The 19 items are grouped into 7 component scores: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The global PSQI score (range 0–21) is calculated by summing

the component scores, whereby a higher score indicates worse sleep condition. A global PSQI _ 5 has been suggested to distinguish poor (PSQI _ 5) from good sleepers (PSQI _ 5), with diagnostic sensitivity of 89.6% and specificity of 86.5% [31]. Internal consistency as measured by Cronbach's _ was 0.83. The Italian versions of the assessment instruments are currently employed in clinical trials (FACT-P), as well as in daily practice of psychiatry/clinical psychology and sleep disorder centers.

2.3. Statistical analysis

The internal consistency reliability of each scale was calculated using Cronbach's _ and the 0.70 standard for group-level comparisons was adopted [32]. According to the Kolmogorov-Smirnov test, a non-normal distribution was observed for BIS (P _ 0.002), while FACT-P, HADS, and PSQI were normally distributed.
Differences between continuous variables were assessed by the Mann-Whitney U test for nonparametric data or the t-test for parametric data when indicated. $_2$ or $_2$ for trend tests were used to compare categorical variables. The Spearman test for nonparametric data or the Pearson test for parametric data were used when indicated to calculate correlations between variables. Multivariate logistic regression was employed to identify independent variables associated with depression. In the logistic regression model, a HADS score of 7 was set as the cut-off value for depression (dependent variable) to discriminate between nondepressive and depressive patients. Among the independent variables, age was considered as a continuous variable, while serum PSA, Gleason score, stage, occupation, living alone, civil status, and education were categorized as described in Table 1. Multivariate logistic regression was also employed to identify independent psychological variables associated with ADT. All statistical tests were two-sided; statistical significance was set at P _ 0.05. Statistical computations were performed using SPSS ver. 16.0 for Windows software (SPSS Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

The study population was 103 patients, 49 (47.6%) of whom had undergone hormone therapy with LH-RH analogues and 54 (52.4%) had not (control group). The control group included 47 low-risk and 2 high-risk patients who had undergone radical prostatectomy and 5 low-risk patients treated with radiation therapy, who declined the recommended hormone therapy due to fear of impotence.
Table 1 summarizes the patient characteristics. The patients referred for adjuvant hormone therapy were slightly older, with a more advanced disease stage and higher Gleason scores and PSA levels than the controls. They were more frequently treated with radiation therapy rather than radical prostatectomy as primary loco-regional therapy. No differences between the 2 groups were observed for occupation, living alone, civil status, education, and time since diagnosis.

3.2. Relationship between depression and other variables

A strong direct correlation emerged between depression score and total FACT-P score (Pearson r 0.61; P = 0.01), with anxiety (Pearson r 0.71; P = 0.0001), and total PSQI score (Pearson r 0.79; P = 0.0001). Conversely, a weak direct correlation was found between depression and BIS score (Spearman r 0.21; P = 0.03). At multivariate regression analysis, however, only FACT-P and anxiety were independently associated with depression (P = 0.003 and P = 0.0001, respectively), whereas BIS and PSQI were not (P = 0.07 and P = 0.52, respectively).

3.3. Anxiety and depression

No differences in anxiety levels between the two groups were observed, whereas the patients receiving hormone therapy were noted to have more severe depression (P = 0.002) (Table 2): 44 (81.5%) patients in the control group had no depression (HADS score = 7) vs. 26 (53.1%) in the ADTtreated group; 6 (11.1%) had moderate depression (HADS score 8–11) vs. 13 (26.5%) in the ADT-treated group; and 4 (7.4%) had severe depression (HADS score = 12) vs. 10 (20.4%) in the ADT-treated group (=$_2$ for trend; P = 0.004). Hormone therapy was significantly associated with depression at multivariate analysis after adjustment for age, stage, Gleason score, as well as demographic and social variables (relative risk, 5.56; 95% confidence interval [CI], 2.10 –14.8; P = 0.001) (Table 3). Only age had an independent predictive role of borderline significance.

3.4. Quality of life

Table 2 presents the FACT-P subscale scores of the ADT-treated patients and the controls. The total FACT-P score was significantly lower (P = 0.001) in the ADT-treated patients than in the controls, as were the subscale scores for physical well-being (P = 0.001), social/family well-being (P = 0.009) and functional well-being (P = 0.0001). The scores for emotional well-being and prostate cancer subscale were fairly similar in both groups.

3.5. Body image scale and sleep disturbance

Table 4 and Table 5 present the scores on the Body image scale and PSQI components, respectively. The total BIS score was consistently higher in the ADT-treated patients than in the controls (P = 0.001), indicating worse self-image perception. Significant differences were observed in all single items, except for self-consciousness of

appearance and satisfaction with appearance when dressed, on which the ADT-treated patients scored significantly higher.
No statistically significant difference emerged between the 2 groups for total PSQI and relevant items, except for the daytime dysfunction ($P = 0.03$) and the sleep quality components (borderline significance; $P = 0.07$), which were worse in the ADT-treated patients than the controls.

3.6. Psychological distresses independently associated with ADT
Since most psychological scales were associated with depression, a multivariate logistic analysis was performed to assess whether these variables were independently associated with ADT. As outlined in Table 6, all the variables except PSQI were independently associated with ADT.

4. Discussion

Androgen-deprivation therapy is increasingly administered for early stages of prostate cancer, exposing men to prolonged periods of treatment. In light of these trends, concerns have been raised about the toxic effects of ADT. Physicians are aware of the metabolic and physical toxicity of ADT, but relatively scarce attention has been paid to its psychological side effects. Both hypogonadism and testosterone deprivation have been associated with depressive disorders in non-neoplastic men [13–15]. The correlation of depression with ADT in prostate cancer patients, however, is more difficult to demonstrate because many depressive effects could plausibly occur secondary to a diagnosis of cancer and the onset of relevant symptoms. In a large-scale series of patients in the linked Surveillance, Epidemiology, and End Results–Medicare database [26] involving either metastatic or apparently disease-free patients, the risk of depression associated with androgen deprivation was substantially abolished after adjustment for variables such as comorbidity, tumor characteristics, and age. In the present study, we evaluated depression and other physical and psychological distresses contributory to depression in a consecutive series of patients who had received loco-regional treatments (radical prostatectomy and radiation therapy) for non-metastatic disease, 48% of whom were receiving ADT and 52% were under follow-up alone. Patients with major comorbidities were excluded from the study to minimize biases. Our ADT-treated patients were slightly older than the controls and, as expected, had a more advanced tumor stage and grade, and were more frequently referred for radiation therapy than prostatectomy as primary local treatment. The 2 groups were well-matched for civil and social status.
Depression strongly correlated with poor quality of life, anxiety, and sleep disorders, substantially confirming previous findings [5,6,23,24,33]. The weak relationship between depression and changes in self body image perception suggests that this distress may be scarcely associated with the depressive symptoms.
The main finding of our study is that depressive symptoms were more frequently observed among the ADTtreated patients. ADT was also strongly associated with diminished quality of life (particularly in the domains of physical well-being, social/family well-being, and functional well-being) and worsening in self body image perception.
Sleep disorders were only marginally affected, whereas no effect on anxiety was observed. Since depression, quality of life and, to a lesser extent, self body image perception were reciprocally correlated, an interesting issue is whether the depressive symptoms in our series were associated directly with testosterone deficiency or indirectly as a consequence of fatigue, physical impairment, and changes in body image related to ADT [34,35]. A multivariate logistic regression analysis showed that depression was independently associated with ADT and this suggests a direct effect of treatment.
The cross-sectional nature of the study did not allow us to discriminate whether the increased frequency of depression among the ADT-treated patients was due to the treatment received or was already present before treatment began. As the 2 populations significantly differed in prognostic factors at baseline condition, this could potentially have contributed to the difference in the occurrence of depression between the groups. It should be noted, however, that the 2 groups had been similarly informed by the physicians about the prospects of disease outcome and that the greater frequency of depression among the ADT-treated patients persisted at multivariate analysis after adjusting for age, stage, Gleason score, as well as demographic and social variables. These observations notwithstanding, the absence of an evaluation of depressive disorders at baseline condition is admittedly the main limitation of the present study.
The multivariate logistic analysis of psychological variables independently associated with ADT, points out that anxiety has a statistically significant inverse correlation with ADT, thus patients submitted to hormone therapy are less likely to have anxiety than those non submitted. Since anxiety and depression are frequently directly correlated, it is difficult to explain this apparently counter-intuitive finding.
It could be hypothesized that men on ADT may be somewhat reassured of being under antineoplastic treatment, while those in follow-up only could be more afraid of a tumor recurrence. This hypothesis needs confirmation in a prospective trial. Depression is notoriously linked to sleep disorders [24], and the strong correlation that emerged between depression and PSQI scores confirms this observation. The interplay of cause and effect has attracted increasing attention, though the underlying pathophysiology remains unclear [36]. Vasomotor symptoms are known to be strong predictors of trouble sleeping [37], which might have been responsible for the insomnia syndrome in our series. Unfortunately, the frequency of hot flushes was not recorded in our series, and this is a further limitation of the present study. ADT, however, was noted to have only a slight effect on sleep disturbances in our series. The relationship

between testosterone and sleep disorders is very complex, and the interaction between the 2 is probably bidirectional, as recently reviewed [19]. A high incidence of insomnia has been observed in men undergoing radical prostatectomy even in the absence of ADT [20], which may explain, at least in part, the lack of a strong effect of ADT on sleep disorders in our series. Epidemiologic data indicate an association between major depressive disorder and increased cardiovascular morbidity and mortality [38,39], suggesting that depression can account, at least in part, for the increased cardiovascular morbidity of ADT [39,40].

The inclusion of a rather homogeneous population of non-metastatic prostate cancer patients and the ability to adjust for potential confounders are the strengths of this study. However, it also has several limitations. As mentioned, it was cross-sectional in design and episodes of hot flushes were not recorded. In addition, serum testosterone was not measured in the controls and was inhibited in the ADT group, so that we were unable to test for correlations between serum testosterone and depression. Moreover, the lack of a follow-up evaluation did not allow us to determine whether the psychosocial findings were related to the adjustment process, which usually normalizes within a few months, or were due to more lasting mental disorders.

5. Conclusion

The present study provides evidence that ADT is associated with depression, worsening in quality of life and altered body image perception, and sleep disturbances. These results extend the impact of ADT into the psychological domain beyond the already available data on its metabolic and physical toxicity, and reinforce the notion that prescribing ADT in apparently healthy men with a longer life expectancy needs to be carefully weighed against the risks of its long-term side effects.

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