Increased Fall Risk in Patients Receiving Androgen Deprivation Therapy for Prostate Cancer

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OBJECTIVE To examine the relationship between the use of androgen deprivation therapy (ADT) and the subsequent risk of falls in men with prostate cancer (PC) by employing a population-based dataset.

METHODS We retrieved the study sample from the Taiwan Longitudinal Health Insurance Database 2005. We included 886 patients with PC who had received ADT as the study group, whereas 862 patients with PC who had not received ADT served as the comparison group. We then individually tracked each study patient for a 3-year period to identify those who subsequently received a diagnosis of a fall. We performed Cox proportional hazard regressions to calculate the hazard ratio (HR) and its corresponding 95% confidence interval (CI) for a fall during the 3-year follow-up period between these 2 groups.

RESULTS The incidence rates of falls per 1000 person-years were 13.37 (95% CI: 9.15~18.88) and 6.44 (95% CI: 3.61~10.63), respectively, for patients with PC who received ADT and those who did not receive ADT. Furthermore, the hazard ratio for a fall during the 3-year follow-up period for patients with PC who had received ADT was 1.95 (95% CI: 1.04~3.66, P = .037) compared to those who had not received ADT after censoring sampled patients who died during the 3-year follow-up period and adjusting for age, geographical location, monthly income, urbanization level, hypertension, diabetes, hyperlipidemia, coronary heart disease, Parkinson's disease, epilepsy, stroke, and mental illness.

CONCLUSION The present findings suggest that patients with PC who had received ADT had an increased risk of falls. UROLOGY 95: 145–150, 2016. © 2016 Published by Elsevier Inc.

Prostate cancer (PC) is the second most common diagnosed malignancy in men worldwide, with an estimated 1.1 million cases reported in 2012.[1] Androgen deprivation therapy (ADT) is the standard treatment for aggressive and advanced PC.[2] ADT includes an orchiectomy, estrogens, antiandrogens, luteinizing hormone-releasing hormone (LHRH) agonists and antagonists.[3,4]

Plenty of studies have demonstrated that ADT can improve disease-free and overall survival when used in combination with radiation for patients with locally advanced PC.[5,6] However, androgens are an important part of the body composition in males as they support lean body mass over fat mass.[7] One study indicated that LHRH agonist therapy increased fat mass by 10% and decreased lean body mass by 3% and also the associated sarcopenic obesity.[8] The reduced muscle mass may be related to the risk of falls.[9]

Globally, falls are the major cause of accidental or unintentional injury and deaths.[10] However, previous findings rarely examined the association between ADT and the risk of falls. To fill in this gap in the literature, the present study aimed to examine the relationship between the use of ADT and the subsequent risk of falls in men with PC by employing a population-based dataset in Taiwan.

METHODS

Database

We retrieved the study sample for this population-based retrospective cohort study from the Taiwan Longitudinal Health Insurance Database 2005 (LHID2005). The LHID2005 includes beneficiary registration files and medical claims data for reimbursement for 1 million individuals randomly selected from all enrollees in the Taiwan National

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Health Insurance program in 2005 (n = 25.68 million). The LHID2005 was created by the Taiwan National Health Research Institute and is provided to researchers in Taiwan for academic purposes. Numerous studies that employed this dataset have been published.[11,12]

Study Sample

This study features a study group and a comparison group. The study sample first included 1932 patients who received a first-time diagnosis of PC (ICD-9-CM code 185, malignant neoplasm of the prostate) in ambulatory care centers or hospitalization between January 1, 2001 and December 31, 2010. We then limited the study sample to patients aged ≥40 years (n = 1897) because of the very low prevalence of PC in the age group of <40 years. We further designated the date of their first ambulatory care visit for receiving ADT, including LHRH agonists, antiandrogens, and estrogens, as the index date for these PC patients who received ADT. On the other hand, for PC patients who did not receive ADT, we designated the first ambulatory care visit in which they received a PC diagnosis as the index date. Thereafter, we further excluded 149 patients who received an orchiectomy (ICD-9-CM procedure codes 623 or 624) during the 3-year follow-up period following their index date. Finally, a total of 1748 PC patients were selected for the study. We defined 886 PC patients who received ADT as the study group, whereas 862 PC patients who did not receive ADT served as the comparison group.

We then individually tracked each study patient for a 3-year period to identify those who subsequently received a diagnosis of a fall (ICD-9-CM External Cause of Injury Codes E880~E888) following the index date.

Statistical Analysis

We conducted statistical analyses in this study using the SAS system (SAS System for Windows, vers. 9.2, SAS Institute). Chi-squared tests were used to investigate differences in sociodemographic characteristics (monthly income and the urbanization level and geographic location of the patient's residence) between PC patients who received and those who did not receive ADT. Many medications may increase the risk of a fall. However, we were incapable of taking all types of different medications into consideration in the study, but instead we adjusted for relevant medical comorbidities in the regression models. These comorbidities included hypertension, diabetes, hyperlipidemia, coronary heart disease, Parkinson's disease, epilepsy, stroke, and mental illness (ICD-9-CM codes 290~299). We further performed Cox proportional hazard regressions to calculate the hazard ratio (HR) and its corresponding 95% confidence interval (CI) for a fall during the 3-year follow-up period between these two groups. Adjustments were made for patients' age, geographic location, monthly income, urbanization level, hypertension, diabetes, hyperlipidemia, coronary heart disease, Parkinson's disease, epilepsy, stroke, and mental illness in regression models. In this study, we found that the proportional hazards assumption was satisfied since the survival curves for both strata (patients who received and those who did not receive ADT) had hazard functions that were proportional over time. We also censored those patients who died during the 3-year follow-up period (448 study sample died, including 247 patients who received ADT [27.9%] and 201 patients who did not receive ADT [23.3%]) (P = .455). We used the conventional two-sided P value of .05 to indicate statistical significance in this study.

RESULTS

Table 1 shows the distribution of demographic characteristics of PC patients according to the use of ADT. We found that PC patients who had received ADT were more likely to be older than those who had not received ADT (74.2 years vs 70.5 years, P < .001). In addition, there were significant differences in geographic region and monthly income between PC patients who had received ADT and those who had not (both P < .001). However, there was no significant difference in the prevalence of comorbidities of hypertension, diabetes, hyperlipidemia, coronary heart disease, Parkinson's disease, epilepsy, and mental illness between these 2 groups. In addition, the mean length of ADT therapy for PC patients who had received ADT was 524 (±439) days during the 3-year follow-up period.

Table 2 presents the incidence of falls among the sampled patients. Among the total sampled patients, the incidence rate of falls per 1000 person-years was 9.99 (95% CI: 7.32~13.24). The incidence rates of falls per 1000 person-years were 13.37 (95% CI: 9.15~18.88) and 6.44 (95% CI: 3.61~10.63), respectively, for PC patients who had received ADT and those who had not received ADT. The log-rank test suggested that PC patients who had received ADT were more likely to have a fall incidence than those who had not received ADT (P = .016). Furthermore, Table 2 reveals that after censoring sampled patients who died during the 3-year follow-up period, the HR for a fall in PC patients who had received ADT was 2.12 (95% CI: 1.14~3.94) compared to those who had not received ADT.

Furthermore, Table 3 shows the adjusted HR for a fall during the 3-year follow-up period between the 2 groups. Cox proportional hazard regressions suggested that the HR for a fall during the 3-year follow-up period for PC patients who had received ADT was 1.95 (95% CI: 1.04~3.66, P = .037) compared to those who had not received ADT after censoring sampled patients who died during the 3-year follow-up period and adjusting for age, geographical location, monthly income, urbanization level, hypertension, diabetes, hyperlipidemia, coronary heart disease, Parkinson's disease, epilepsy, stroke, and mental illness.

DISCUSSION

Prior studies have reported that ADT may lead to a hypogonadal condition,[2] reduce the quality of life,[13] cause or exacerbate anemia,[2,14] increase risk for diabetes,[8,15] and

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