ORIGINAL RESEARCH—ONCOLOGY

Testosterone Replacement Therapy Following the Diagnosis of Prostate Cancer: Outcomes and Utilization Trends

Alan L. Kaplan, MD,* Quoc-Dien Trinh, MD,† Maxine Sun, PhD,‡ Stacey C. Carter, MD,* Paul L. Nguyen, MD,§ Ya-Chen Tina Shih, PhD,¶ Leonard S. Marks, MD,* and Jim C. Hu, MD, MPH*

*Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; †Center for Surgery and Public Health, Division of Urologic Surgery, Brigham and Women's Hospital, Boston, MA, USA; ‡Cancer Prognostics Health Outcomes Unit, University of Montreal Health Centre, Montreal, QC, Canada; §Department of Radiation Oncology, Brigham and Women's Hospital, Boston, MA, USA; ¶Section of Hospital Medicine, Department of Medicine Program in the Economics of Cancer, University of Chicago, Chicago, IL, USA

DOI: 10.1111/jsm.12429

ABSTRACT

Introduction. Late-onset hypogonadism may impair quality of life and contribute to metabolic and cardiovascular comorbidity in aging men. Testosterone replacement therapy is effective in treating hypogonadism. However, for the millions of men with a history of prostate cancer, exogenous testosterone has long been considered contraindicated, even though little data in such men are available. Clarification of this safety issue could allow treatment to be considered for a sizeable segment of the aging male population.

Aim. The aim of this study is to examine population-based utilization and impact of testosterone replacement therapy in men with prostate cancer.

Methods. Using linked Surveillance, Epidemiology, and End Results-Medicare data, we identified 149,354 men diagnosed with prostate cancer from 1992 to 2007. Of those, 1,181 (0.79%) men received exogenous testosterone following their cancer diagnosis. We used propensity scoring analysis to examine the effect of testosterone replacement on the use of salvage hormone therapy and overall and prostate cancer-specific mortality.

Main Outcome Measures. We assessed overall mortality, cancer-specific mortality, and the use of salvage hormone therapy.

Results. Following prostate cancer diagnosis, testosterone replacement was directly related to income and educational status and inversely related to age (all $P < 0.001$). Men undergoing radical prostatectomy and men with well-differentiated tumors were more likely to receive testosterone (all $P < 0.001$). On adjusted analysis, testosterone replacement therapy was not associated with overall or cancer-specific mortality or with the use of salvage hormone therapy.

Conclusions. In this population-based observational study of testosterone replacement therapy in men with a history of prostate cancer, treatment was not associated with increased overall or cancer-specific mortality. These findings suggest testosterone replacement therapy may be considered in men with a history of prostate cancer, but confirmatory prospective studies are needed. **Kaplan AL, Trinh QD, Sun M, Carter SC, Nguyen PL, Shih YCT, Marks LS, and Hu JC. Testosterone replacement therapy following the diagnosis of prostate cancer: Outcomes and utilization trends. J Sex Med 2014;11:1063–1070.**

Key Words. Testosterone Replacement Therapy; Prostate Cancer; Late-Onset Hypogonadism; Androgen Replacement; Testosterone Deficiency Syndrome

Introduction

Hypogonadism is highly prevalent in middle-aged men and may significantly impair quality of life [1]. Up to 25% of elderly men experience hypogonadism, and the incidence rises with increasing age [2–4]. These men have lower muscle mass, bone mineral density, and are in

poorer overall health [5,6]. Testosterone replacement therapy (TRT) is effective in treating the symptoms and ameliorating metabolic consequences of hypogonadism [5,7–9]. TRT improves muscle mass, bone mineral density, mood, and sexual performance [5,7,8]. Given the strong association between prostate cancer incidence and increasing age, those men at highest risk for prostate cancer are also at highest risk for hypogonadism [9].

Exogenous testosterone has long been thought to promote prostate cancer growth [1,10]. Huggins' et al. showed that testosterone enhanced the rate of prostate cancer growth in dogs [11]. Fowler et al. found that administering testosterone in the presence of metastatic prostate cancer led to disease progression in 87% of men [12]. Based on these historical findings, known prostate cancer—treated or otherwise—is considered by many clinicians to be an absolute contraindication to TRT.

Recent studies suggest that exogenous testosterone in prostate cancer survivors may be safer than previously assumed, although cohort sizes were small in reported experiences [9]. The safety profile of TRT in men with a history of prostate cancer is not well established. Therefore, we sought to characterize the utilization, patterns of care, and outcomes of TRT in men with a history of prostate cancer using a population-based cohort.

Materials and Methods

Data Source

The University of California Los Angeles Institutional Review Board approved this study. Patient-specific data were de-identified, and consent requirements were waived. We analyzed Surveillance, Epidemiology, and End Results (SEER)-Medicare data comprised of linked population-based cancer registries from 20 SEER regions with Medicare administrative data [13]. SEER-Medicare linked data captures nearly 97% of new cancer diagnoses in the United States and collects patient demographic, tumor characteristic, and initial treatment course data [14].

Study Cohort

We identified 348,372 men, aged 65 years or older, diagnosed with prostate cancer between 1991 and 2007. To avoid unreliable claims submissions, we excluded 113,844 men that were enrolled in a health maintenance organization or who were not enrolled in both Medicare part A and B throughout the duration of our study period. To properly assess comorbidity, an additional 20,060 subjects lacking 1 year of precancer diagnosis data were excluded. After complete exclusion criteria were applied, the remaining cohort consisted of 149,354 subjects with prostate cancer. The cohort was divided into those that received TRT (n = 1,181) following prostate cancer diagnosis and those that did not (n = 148,173). TRT usage was identified by the presence of Physicians Current Procedural Terminology Coding System 4th edition (CPT-4) for injection based (J0900, J1060, J1070, J1080, J2320, J3120, J3130, J3140, J3150) and subcutaneous pellet (S0189) testosterone formulations. Topical formulations of TRT were not captured in this analysis.

Control Variables

Age (65–69, 70–74, ≥75 years) was obtained from the Medicare denominator file, whereas race (white/non-Hispanic, black/non-Hispanic, Hispanic, Asian/non-Hispanic), SEER region, education level and household income, population density (urban vs. rural), and tumor characteristic data were obtained from the SEER registry. We combined the Hawaii and rural Georgia SEER registries because of the small number of cases. Medical comorbidity was assessed using the Klabunde modification of the Charlson index based on inpatient, outpatient, and physician services utilized in the year prior to prostate cancer diagnosis [15]. Healthcare accessibility, specifically Medicare-covered preventative testing (e.g., cholesterol screening, influenza vaccination, colonoscopy) and frequency of prostate-specific antigen (PSA) screening prior to prostate cancer diagnosis, may influence stage and grade at diagnosis as well as survival outcomes. We captured the use of these preventive services through Medicare data. Treatment modality was captured by associated CPT-4 procedure code.

Outcomes

We examined prostate cancer-specific outcomes (biopsy tumor grade, clinical stage, initial treatment modality, and the need for salvage androgen deprivation therapy [ADT]) as well as disease-specific and overall survival on the basis of TRT exposure. The use of ADT was identified as previously described [16].