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Patterns of androgen deprivation therapies among men diagnosed with localised prostate cancer: A population-based study

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Abstract ***Aim:*** Many men diagnosed with localised prostate cancer will eventually be treated with androgen deprivation therapy (ADT). ADT is associated with adverse effects and its timing is controversial. Data on patterns of use are scarce. We describe patterns of ADT use, defined as castration (medical and surgical) or antiandrogen monotherapy initiated after primary treatment, in a population-based cohort.

Methods and materials: Data were extracted from the population-based Prostate Cancer data Base Sweden (PCBaSe). Totally 45,147 men diagnosed between 1997 and 2009 with clinical stage T1–2, N0–NX, M0–MX and prostate specific antigen (PSA) < 50 ng/ml without primary ADT were included. Outcomes in the period 2006 through 2010 were analysed using a period analysis approach.

Results: The cumulative incidence of castration at 10 years after diagnosis was 11.6% (95% confidence interval (CI), 11.0–12.2%). The corresponding proportion of antiandrogen monotherapy was 10.8% (95% CI, 10.2–11.4%). Castration was the dominant therapy among men on deferred treatment. The probability of receiving castration rather than antiandrogen monotherapy increased with age. Estimated median durations of castration ranged from

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4 years in the deferred treatment high-risk group to 17 years in the prostatectomy low-risk group. The main limitation was the lack of information on progression to metastatic disease and PSA at the time for initiation of ADT.

Conclusion: When initiated early after curative treatment, the duration of castration can be decades. The findings indicate that more accurate tools are necessary to guide which men should be selected for ADT as secondary treatment.

1. Introduction

Androgen deprivation therapy (ADT) plays a major role in the treatment of prostate cancer, but accurate timing is challenging to define [1]. Overuse of ADT is essential to avoid due to the side-effects. For castration these include unwanted effects on sexual function, bone mineral density, lipid metabolism and insulin sensitivity, which results in increased morbidity and decreased quality of life [2,3]. Antiandrogen monotherapy (bicalutamid 150 mg/day) is approved in Sweden as monotherapy or adjuvant therapy. Antiandrogens block the effect of androgens on the cancer cells while circulating testosterone is preserved. They have been found to have has less morbidity and less unwanted side-effects, especially on sexual function [4–7]. There is no evidence of benefit from ADT for localised cancer [8–10], but studies have nevertheless reported an increased use of castration as primary treatment for localised disease [11,12]. However, little is known about the patterns of ADT used as secondary treatment.

The aim of this study was to investigate the patterns of use for ADT defined as castration (medical and surgical) or antiandrogen monotherapy initiated after primary curative treatment or deferred treatment in a population-based cohort. We investigated the cumulative incidence of ADT and the median duration of castration for men initially diagnosed with localised disease. In addition, we investigated differences in ADT approach (castration versus antiandrogen monotherapy) due to primary treatment, age, educational level and comorbidity.

2. Materials and methods

2.1. Study population and data collection

Our data were extracted from the Prostate Cancer data Base Sweden (PCBaSe), which comprises all cases of prostate cancer diagnosed since 1996 in the National Prostate Cancer Register of Sweden (NPCR). The NPCR holds information about prostate specific antigen (PSA) level at the time of diagnosis, TNM staging, tumour differentiation and primary treatment as reported within 6 months of diagnosis. It comprises more than 97% of all prostate cancer cases covered by the Swedish Cancer Registry, to which the underreporting of prostate cancer is less than 3.7% [13].

Through the Swedish personal identity number, PCBaSe links the NPCR to other population-based registries. In this study we used data from the Prescribed Drug Register, the National Patient Register, the Cause of Death Register and LISA (a nation-wide database on socioeconomic factors). PCBaSe has been described in detail previously [13].

2.2. Study design

We selected all men in PCBaSe with localised prostate cancer (clinical stage T1–T2, N0–NX, M0–MX, serum levels of PSA < 50 ng/ml), and with a date of diagnosis between 1997 and 2009. All men with primary ADT (medical castration, surgical castration or antiandrogen monotherapy) or ADT during the run-in period described below were excluded, as were men who died or emigrated before the start of the Prescribed Drug Register (started 1st July 2005).

The men were categorised according to primary treatment, separating the cohort into the groups of radical prostatectomy, radiotherapy and deferred treatment. Radiotherapy comprised external beam therapy and brachytherapy. Deferred treatment included both active surveillance and watchful waiting, as these strategies were not separately registered in NPCR before 2007. Active surveillance denotes a strategy with close follow-up and curative treatment in cases of progression, whereas watchful waiting men with limited life expectancy are treated symptomatically when the disease progresses.

We subdivided the cohort into three risk categories for each treatment group, based on a modification of the National Comprehensive Cancer Network (NCCN) categorisation while only considering localised cancer [14]. Our risk groups were defined as: (1) Low-risk: Clinical stage T1–T2, Gleason score 2–6 and PSA below 10 ng/ml; (2) Intermediate-risk: Clinical stage T1–T2, Gleason score 7 and/or PSA 10–20 ng/ml; (3) High-risk: Clinical stage T1–T2, Gleason score 8–10 and/or PSA 20–50 ng/ml. Comorbidities were classified according to the Charlson Comorbidity Index by using data from the National Patient Register [15]. Educational level was divided into three groups based on years of schooling: Low ($\leqslant$9 years), middle (10–12 years) and high ($\geqslant$13 years)

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