Clinical Oncology xxx (2017) 1–6

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

The Relationship between Hot Flashes and Testosterone Recovery after 12 Months of Androgen Suppression for Men with Localised Prostate Cancer in the ASCENDE-RT Trial

M. Dosani *†, W.J. Morris *†, S. Tyldesley *†, T. Pickles *†

* Department of Radiation Oncology, Vancouver Centre, BC Cancer Agency, Vancouver, British Columbia, Canada
† Division of Radiation Oncology and Developmental Radiotherapeutics, Department of Surgery, University of British Columbia, Vancouver, British Columbia, Canada

Received 22 April 2017; accepted 15 June 2017

Abstract

Aims: This study describes the proportion of men who experienced hot flashes (flashes), and the testosterone level at onset, peak frequency and cessation of flashes after 12 months of androgen deprivation therapy (ADT) in men undergoing curative-intent external beam radiation therapy (± brachytherapy boost). We also aimed to characterise testosterone recovery in this population.

Materials and methods: This was a pre-specified secondary analysis of the ASCENDE-RT clinical trial. Three hundred and ninety-eight men were randomised. All received 12 months of ADT. The presence and frequency of flashes were patient reported. Cessation of flashes was defined as the first date a patient reported resolution of this symptom. Testosterone recovery was defined as any single serum testosterone above the threshold of 5, 7.5 or 10 nmol/l.

Results: The median age and follow-up were 68 years and 6.1 years. Flashes were reported in 93% of men. Flashes began and reached peak frequency at a median time of 4.0 months from the first luteinizing hormone-releasing hormone injection when testosterone levels had fallen to castrate. The median time to cessation of flashes was 7.6 months after the cessation of ADT (last injection + 3 months), when the median testosterone had risen to 5.7 nmol/l. A resolution of flashes was reported in 99% of patients. Baseline testosterone was available in 338 patients (85%). The median baseline testosterone was 13.2 nmol/l. The median (95% confidence interval) time of testosterone recovery to thresholds of 5 nmol/l, 7.5 nmol/l and 10 nmol/l were 9 (9–10) months, 13 (10–15) months and 18 (17–19) months from the cessation of ADT. At the time of censor, 96, 94 and 91% of patients had recovered testosterone to thresholds of 5, 7.5 and 10 nmol/l.

Conclusion: Flashes occur at castrate levels of testosterone, with cessation of hot flashes antedating full recovery of testosterone in most patients. Rates of testosterone recovery after 12 months of ADT exceed 90%, although it can be delayed.

Key words: Androgen deprivation therapy; brachytherapy; external beam radiotherapy; hot flashes; prostate cancer; testosterone recovery

Introduction

Androgen suppression using androgen deprivation therapy (ADT) is a common treatment in the management of prostate cancer. When used in the neoadjuvant or adjuvant setting, the goal is for temporary suppression of testosterone.

Previous investigations of testosterone recovery after ADT have shown that the time to recovery of testosterone can far exceed the prescribed duration of ADT [1–3], especially when 3-monthly luteinizing hormone-releasing hormone (LHRH) agonist injections are used (as opposed to monthly preparations) [1,4].

Although ADT is associated with improved outcomes for some patients with prostate cancer, it is associated with multiple, although usually temporary, side-effects, including erectile dysfunction, loss of libido, hot flashes, metabolic changes (which may contribute to the risk of serious medical comorbidities, including diabetes, hypertension and coronary artery disease), anaemia, decreased energy, decreased bone mineral density, gynecomastia and hair changes [5]. Patients are frequently counselled to expect these side-effects for the duration of ADT, but given

Author for correspondence: M. Dosani, c/o Aida-Castro-Chan, BC Cancer Agency, Vancouver Centre, 600 W 10th Ave, Vancouver, BC V5Z 4E6, Canada. Tel: +1-604-877-6000.
E-mail address: Maryam.dosani@bccancer.bc.ca (M. Dosani).

http://dx.doi.org/10.1016/j.clon.2017.06.009
0936-6555/

emerging information on the time to testosterone recovery and the lack of known testosterone values at which side-effects occur, it is important to assess the time course and rates of recovery of side-effects associated with ADT for proper patient selection [6] and counselling.

The recent Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) clinical trial [7] investigated biochemical progression-free survival in a randomised trial comparing two methods of dose escalation for intermediate- and high-risk prostate cancer. In this trial, testosterone was measured and hot flashes (flashes) were self-reported prospectively at regular intervals with a standardised questionnaire. The assessment of flashes was included because it provides a quantifiable end point, it is a common symptom of ADT and is an important contributor to quality of life in men treated with ADT [8].

The aims of our investigation were: (a) to assess the time to onset, peak frequency and cessation of flashes in men receiving 1 year of ADT; (b) to prospectively evaluate testosterone recovery in a cohort of patients with unfavourable risk localised prostate cancer undergoing ADT and external beam radiotherapy plus dose-escalated external beam radiotherapy versus low dose rate brachytherapy boost.

Materials and Methods

This investigation was a secondary analysis of the ASCENDE-RT clinical trial [7], in which 398 patients with localised unfavourable risk prostate cancer were randomised to receive 46 Gy/23 fractions of pelvic irradiation followed by dose-escalated external beam radiotherapy boost to a dose of 32 Gy/16 fractions or low dose rate brachytherapy boost (minimum peripheral dose 115 Gy). All patients, regardless of randomisation, received ADT with 12 months of LHRH agonist, given as 3 month depot injections of either buserelin acetate 9.56 mg or leuprolide acetate 22.5 mg. Four weeks of concurrent oral non-steroidal anti-androgen (flutamide 250 mg three times a day or bicalutamide 50 mg daily) were given at the initiation of ADT. Cessation of ADT was defined as the date of last LHRH agonist injection + 3 months. The primary outcome of ASCENDE-RT was biochemical progression-free survival, which is reported elsewhere [7].

Hot Flashes

Patients were asked to self-report the presence (yes or no) and daily frequency (<5, 5–9, 10–20, ≥ 20) of flashes at 4 monthly intervals until 1 year, 6 monthly intervals until 5 years and yearly thereafter. All patients were included in the flash analysis, regardless of recorded baseline testosterone values. The time to initiation or to the peak frequency of flashes was defined as the time from the first injection of ADT to the first report or to the report of the peak frequency of flashes, respectively. Initial cessation of flashes was defined as the first date a patient, who previously experienced flashes, reported resolution of this symptom (regardless of subsequent reports of flashes). The time to cessation of flashes was determined from the date of the last LHRH injection + 3 months. The testosterone level may not have been measured on the same date as the clinic visits in which flashes were reported. In such instances, a corresponding testosterone level was selected if it was measured within 30 days of the clinic visit. Patients were censored at the date of last flash assessment or at the date of re-initiation of ADT (for prostate-specific antigen failure). Use of medications for flashes was prospectively recorded.

Testosterone Recovery

In the trial, testosterone was measured prospectively, before the initiation of ADT, then at 2, 4, 6, 8, 12, 15, 18, 21 and 24 months. After 24 months, testosterone was measured q6 monthly. The analysis of testosterone recovery was restricted to patients with a recorded baseline testosterone above the thresholds for recovery (5, 7.5 and 10 nmol/l). The thresholds of 5 and 10 nmol/l were selected to represent a minimum testosterone level thought to be required for normal physiological functions in most men, based on preliminary data [1] and the most common lower threshold for normal in laboratory assays, respectively. The threshold of 7.5 nmol/l was selected as an intermediate value. Testosterone was considered recovered when a single post-ADT (last LHRH injection + 3 months) testosterone measurement was greater than or equal to the threshold, regardless of subsequent testosterone measurements. Patients were censored at the date of last testosterone measurement or the date of re-initiation of ADT.

Statistical Analysis

The statistical analysis was performed using SPSS software version 14.0 (IBM, New York, USA). An actuarial outcome analysis was carried out using the Kaplan–Meier method, with the Log-rank test used to compare groups.

This research had institutional Research Ethics Board approval.

Results

Patients had a median age of 68 years. The median follow-up was 6.1 years (Table 1).

Flash data were available in 392 patients (98%). Flashes were reported in 93% of men during the investigation. Flashes were first reported at a median of 4.0 months from the first LHRH injection, when testosterone had fallen to castrate. The peak frequency of flashes also occurred at this time and testosterone level. The peak frequency of flashes (amongst those experiencing flashes) was <5 flashes per day in 38% of men, 5–9 flashes/day in 38% of men, 10–19 flashes per day in 17% of men and ≥ 20 flashes per day in 6% of men. The median time of cessation of flashes was 7.6 months after the cessation of ADT, when the median testosterone had risen to 5.7 nmol/l (Figure 1).

Please cite this article in press as: Dosani M, et al., The Relationship between Hot Flashes and Testosterone Recovery after 12 Months of Androgen Suppression for Men with Localised Prostate Cancer in the ASCENDE-RT Trial, Clinical Oncology (2017), http://dx.doi.org/10.1016/j.clon.2017.06.009