ELSEVIER

Brachytherapy ■ (2018) ■

BRACHYTHERAPY

A Phase II trial of 8 weeks of degarelix for prostate volume reduction: Efficacy and hormonal recovery

M.A. Korzeniowski[1], J.M. Crook[2,*], D. Bowes[3], M. Gaztañaga[4], A. Ots[5], J. Jazwal[6], J. Rose[7], A. Tétreault-Laflamme[8], L. Pilote[9], R. Halperin[2], D. Kim[2], D. Petrik[2], C. Araujo[2], F. Bachand[2]

[1]*Kingston Health Sciences, Queen's University, Kingston, Ontario, Canada*
[2]*British Columbia Cancer Agency, Center for the Southern Interior, Kelowna, British Columbia, Canada*
[3]*Nova Scotia Cancer Centre, Halifax, Nova Scotia, Canada*
[4]*Departmento Oncologia Radioterapia, Universidad Complutense Madrid, Madrid, Spain*
[5]*Clinical Oncology Department, United Lincolnshire Hospitals, Lincoln, UK*
[6]*BC Cancer Agency, Surrey, British Columbia, Canada*
[7]*BC Cancer Agency, Abbotsford Centre, Abbotsford, British Columbia, Canada*
[8]*Centre Hospitalier Universitaire de Sherbrook, Sherbrook, British Columbia, Canada*
[9]*Centre Hospitalier Universitaire de Quebece, Quebec City, Quebec City, Canada*

ABSTRACT

PURPOSE: The purpose of this study was to determine the efficacy of 8 weeks of degarelix for prostate downsizing before interstitial brachytherapy. We also report associated toxicity and the time course of endocrine recovery over the following 12 months.

METHODS AND MATERIALS: Fifty patients were accrued to an open-label Phase II clinical trial (www.clinicaltrials.gov ID NCT01446991). Baseline prostate transrectal ultrasound (TRUS) was performed on all patients followed by degarelix administration and a repeat TRUS at Week 8. Brachytherapy was performed within 4 weeks of the 8-week TRUS for all patients who achieved suitable downsizing.

RESULTS: The median prostate volume was reduced from 65.0 cc (interquartile range [IQR]: 55.2−80.0 cc) to 48.2 cc at 8 weeks (IQR: 41.2−59.3 cc), representing a median decrease of 26.2% (IQR: 21−31%). Functional recovery of testosterone within an age-adjusted normal range occurred at a median of 34.1 weeks (IQR: 28.2−44.5 weeks) from the date of the final injection. Despite this recovery, follicle-stimulating hormone and luteinizing hormone levels remained abnormally elevated throughout 12 months. Quality-of-life implications are discussed.

CONCLUSIONS: Degarelix is effective for prostate downsizing before prostate brachytherapy with a median volume decrease of 26.2% by 8 weeks. Despite the short course of treatment and eventual testosterone recovery, follicle-stimulating hormone and luteinizing hormone remain elevated beyond 12 months. Further investigation with randomized comparisons to other hormonal agents is warranted.

Keywords: Prostate neoplasms; Degarelix; Brachytherapy; Testosterone; Quality of life

Introduction

Permanent seed low-dose-rate (LDR) and temporary high-dose-rate (HDR) interstitial brachytherapy are highly effective treatment options for clinically localized prostate cancer (1−7). However, pubic arch interference (PAI) may limit access to the anterior and lateral portions of the gland in patients with larger prostates. These individuals are also at increased risk of postimplant urinary retention (8−10), another reason for prostate size reduction.

Received 13 November 2017; received in revised form 20 December 2017; accepted 20 December 2017.

Financial disclosure: This study was sponsored by an unrestricted grant from Ferring Pharmaceuticals. Ferring Pharmaceuticals had no role in data collection, analysis, or article preparation.

Conflict of interest: None of the authors declare a conflict of interest concerning any of the materials in this article.

* Corresponding author. British Columbia Cancer Agency, Center for the Southern Interior, 399 Royal Avenue, Kelowna, British Columbia, Canada, V1Y5L3. Tel.: +1-250-712-3958; fax: +1-250-712-3911.

E-mail address: jcrook@bccancer.bc.ca (J.M. Crook).

1538-4721/$ - see front matter
https://doi.org/10.1016/j.brachy.2017.12.005

Preoperative imaging identifies potential PAI (11), permitting prostate downsizing with androgen deprivation therapy (ADT) before brachytherapy, commonly using luteinizing hormone−releasing hormone (LHRH) agonists, with or without nonsteroidal antiandrogens. Numerous retrospective studies report median prostate volume reduction of 30% at 3 months (12−17). However, ADT is associated with metabolic side effects including sarcopenic obesity, decreased insulin sensitivity, and altered lipid profiles (18). Prolonged male hypogonadism is an independent risk factor for the development of metabolic syndrome (19), and LHRH agonists contribute to this by suppressing testosterone. Shorter courses of ADT (18 vs. 36 months) have less impact on quality of life (QOL) without affecting efficacy (20). However, Crook *et al.* (21) found that even 3 to 8 months of neoadjuvant ADT resulted in persistently castrate testosterone levels in some men. In scenarios lacking oncological benefit from ADT, the undesirable side effects and adverse effects on QOL are preferably avoided. Thus, there is a need to consider other agents that may achieve the required prostate downsizing with less morbidity and impact on QOL.

Other strategies, including the use of an antiandrogen alone or 5-α reductase inhibitor alone, are associated with less sexual dysfunction (22) but may be less effective with some studies reporting only 7−17% volume reduction (15, 23, 24). Antiandrogens are also associated with worse sexual QOL scores (24) and high rates of gynecomastia (22).

Degarelix is a novel agent that functions as a direct gonadotropin-releasing hormone (GNRH) antagonist, blocking the GNRH receptors and preventing the pituitary release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Potential advantages of treatment with degarelix include rapid testosterone suppression, without an associated testosterone flare. Two recent randomized trials (25, 26) have demonstrated testosterone suppression by Day 3 of treatment and noninferiority in maintaining castrate levels. Randomized trials have demonstrated that degarelix produces similar total prostate volume reduction at 12 weeks compared to goserelin and perhaps improved lower urinary tract symptoms (27, 28). Thus, degarelix may have a role in prostate downsizing before brachytherapy, especially if a more favorable toxicity profile is demonstrated.

The purpose of this study was to assess the efficacy of degarelix in reducing prostate volume before transperineal interstitial prostate brachytherapy and to report functional outcomes and endocrine recovery.

Methods and materials

Recruitment

This was an open-label Phase II clinical trial (www.clinicaltrials.gov ID NCT01446991), conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000. The Ethics Review Board of the University of British Columbia and BC Cancer Agency approved the study. Signed written consent was obtained from all the study participants.

Patients were recruited from referrals to the BC Cancer Agency, Centre for the Southern Interior for consideration of either LDR or HDR prostate brachytherapy. All patients had a prostate volume greater than 40 cc at the time of evaluation with transrectal ultrasound (TRUS).

Patients' eligibility

Patients had a histologic diagnosis of prostate cancer and were eligible for trial entry under one of two arms, either favorable or unfavorable. Favorable arm patients had evidence of PAI, had favorable intermediate-risk prostate cancer (<cT2c and either Gleason score 6/prostate-specific antigen [PSA] 10−15 ng/mL or Gleason score 7/PSA < 10 ng/mL), and were otherwise suitable for brachytherapy as monotherapy. Patients were eligible under the unfavorable arm with prostate volume >40 cc requiring ADT for oncologic reasons as determined by the treating physician. These patients did not require evidence of PAI and continued ADT beyond 8 weeks, but prostate volume reduction was assessed at 8 weeks for consistency. All patients were considered otherwise suitable for brachytherapy and had selected this treatment modality. The issue of PAI was decided by the treating oncologist at the time of TRUS.

All patients required a baseline-planning TRUS (BK Ultrasound; Peabody, MA), positioned in dorsal lithotomy with images acquired at 5 mm intervals or less. Contouring was performed by the treating radiation oncologist on Vitesse 3 or VariSeed 8 platforms (Varian, Palo Alto, CA) and independently verified by J.M.C. and M.A.K. The prostate and transition zone volumes were calculated using TRUS-based step-section planimetry. Leg positioning angles, interpatellar distance, and ultrasound probe angles were recorded for reproducibility at each subsequent TRUS.

Treatment and followup

All patients received a loading dose of degarelix of 240 mg as two subcutaneous injections of 120 mg after consent and enrollment. The subsequent maintenance dose was 80 mg subcutaneous every 4 weeks, the duration depending on the oncologic risk group and TRUS findings. Favorable arm patients received their loading dose of degarelix and one 80 mg maintenance dose at 4 weeks. TRUS was repeated at Week 8. Those with adequate downsizing proceeded with brachytherapy within 4 weeks, and no further degarelix was administered. If the patient was unsuitable for implantation at Week 8, a second maintenance dose of 80 mg of degarelix was administered and TRUS was repeated at Week 12. If downsizing was still