Clinical Oncology 25 (2013) 190–196

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Neoadjuvant Androgen Deprivation Therapy for Prostate Volume Reduction, Lower Urinary Tract Symptom Relief and Quality of Life Improvement in Men with Intermediate- to High-risk Prostate Cancer: A Randomised Non-inferiority Trial of Degarelix versus Goserelin plus Bicalutamide

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Received 6 June 2012; received in revised form 2 August 2012; accepted 14 August 2012

Abstract

Aims: The treatment of intermediate- to high-risk prostate cancer with radical radiotherapy is usually in combination with neoadjuvant androgen deprivation therapy. The aim of the present trial was to investigate whether degarelix achieves comparable efficacy with that of goserelin plus bicalutamide as neoadjuvant therapy before radiotherapy.

Materials and methods: The study was a randomised, parallel-arm, active-controlled, open-label trial in 244 men with a UICC prostate cancer TNM category T2b–T4, N0, M0, Gleason score ≥7, or prostate-specific antigen ≥10 ng/ml and a total prostate volume >30 ml, who were scheduled to undergo radical radiotherapy and in whom neoadjuvant androgen deprivation therapy was indicated. Eligible patients received treatment with either monthly degarelix (240/80 mg) or goserelin (3.6 mg) for 12 weeks, the latter patients also receiving bicalutamide (50 mg) for 17 days initially. The primary efficacy measure was the mean percentage reduction in total prostate volume from baseline at week 12 measured by transrectal ultrasound. The severity and relief of lower urinary tract symptoms were assessed by the International Prostate Symptom Score questionnaire. Quality of life was assessed by the eighth question of the International Prostate Symptom Score. About 50% of the patients had moderate to severe lower urinary tract symptoms at baseline.

Results: The total prostate volume decreased significantly from baseline to week 12 in both treatment groups, reaching −36.0 ± 14.5% in degarelix-treated patients and −35.3 ± 16.7% in goserelin-treated patients (adjusted difference: −0.3%; 95% confidence interval: −4.74; 4.14%). At the end of the therapy, more degarelix- than goserelin-treated patients reported International Prostate Symptom Score decreases of ≥3 points (37% versus 27%, $P = 0.21$). In addition, in patients with a baseline International Prostate Symptom Score of ≥13, the magnitude of the decrease was larger in degarelix- ($n = 53$) versus goserelin-treated patients ($n = 17$) (6.04 versus 3.41, $P = 0.06$).

Conclusions: The efficacy of degarelix in terms of prostate shrinkage is non-inferior to that of goserelin plus bicalutamide. The added benefits of degarelix in terms of more pronounced lower urinary tract symptom relief in symptomatic patients could be the reflection of differences in the direct effects on extra-pituitary receptors in the lower urinary tract [Clinicaltrials.gov ID: NCT00833248].

Key words: Prostate cancer; prostate volume reduction; short-term androgen deprivation; urinary symptom management

Introduction

The treatment of intermediate- to high-risk prostate cancer with radiotherapy is usually in combination with

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0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2012.09.010

neoadjuvant androgen deprivation therapy (ADT). Apart from the radiobiologically synergistic action between ADT and radiotherapy [1], one of the reasons for neoadjuvant ADT, in patients in all risk groups, is to decrease prostate volume before radiotherapy, thus decreasing the dose in critical organs, which results in a safer and more effective procedure [2]. Neoadjuvant ADT before radiotherapy can lead, on average, to a 25–30% reduction in prostate size [3,4].

The clinical benefits of neoadjuvant ADT are highlighted by several recent reports. In the Radiation Therapy Oncology Group 86-10 study, radiotherapy with or without combined androgen blockade (goserelin and flutamide) in men with bulky localised and locally advanced prostate cancer resulted in a significantly reduced 5 year incidence of local progression versus radiotherapy alone [5]. Similarly, the 5 year progression-free survival with normal prostate-specific antigen (PSA) levels was significantly greater with neoadjuvant ADT than without. Recent results from the same study showed a trend to improved 10 year overall survival in the neoadjuvant ADT arm, although the differences were not statistically significant [6]. In addition, disease-specific mortality, distant metastasis, disease-free survival and biochemical failure were all significantly superior in the neoadjuvant ADT arm. In the Trans-Tasman Radiation Oncology Group 96.01 trial, 10 year data showed that 3 and 6 months of neoadjuvant ADT (goserelin and flutamide) in men with localised and locally advanced prostate cancer resulted in significantly reduced PSA progression, local progression and improved event-free survival compared with radiotherapy alone [7].

Gonadotrophin-releasing hormone (GnRH) agonists are widely used but cause an initial stimulatory effect on GnRH receptors, which results in a rapid release of gonadotrophins and testosterone. This testosterone surge ('flare') may not only delay the onset of androgen deprivation, but also carry a risk of complications, such as spinal cord compression, bladder outlet obstruction and exacerbation of pain in high-risk metastatic patients [8]. To avoid such complications, anti-androgens are commonly co-administered with the GnRH agonist [9]. In contrast to agonists, the blockade of GnRH receptors by antagonists such as degarelix results in a rapid, marked and sustained suppression of testicular testosterone production without the need for concomitant medication [10]. There are currently no published comparative data of the use of a GnRH antagonist as compared with the combined use of a GnRH agonist and anti-androgens in the neoadjuvant setting [11].

The primary objective of the present trial was to compare the effect of 3 month neoadjuvant therapy with degarelix versus goserelin plus bicalutamide, on total prostate volume (TPV) reduction in men with intermediate- to high-risk prostate cancer who were scheduled to undergo subsequent radiotherapy. Secondary objectives included the effect on lower urinary tract symptom (LUTS) relief and changes of quality of life related to urinary symptoms.

Materials and Methods

Trial Design and Patients

The trial was a randomised, parallel-arm, active-controlled, open-label trial. Main inclusion criteria were: UICC prostate cancer TNM category T2b-T4, N0, M0, Gleason score $\geq$7, or PSA $\geq$10 ng/ml; TPV >30 ml; scheduled to undergo radical radiotherapy treatment and in whom neoadjuvant ADT was indicated. Major exclusion criteria were previous treatment for prostate cancer or transurethral resection of the prostate; use of a urethral catheter; treatment with a 5-alpha reductase inhibitor (finasteride or dutasteride) in the past 12 and 16 weeks, respectively; or treatment with an alpha-adrenoceptor blocker in the past 4 weeks. The trial was approved by the appropriate ethical committees related to the institutions in which it was carried out and all patients gave written consent to participate.

Treatments

Eligible patients were randomised in a 3:1 ratio to receive treatment with degarelix or goserelin for 12 weeks. For patients in the degarelix group, a starting dose of 240 mg (40 mg/ml) was given on day 0 [10]. The second and third doses (maintenance doses) of 80 mg (20 mg/ml) were given on days 28 and 56, respectively. For patients in the control arm, once-daily treatment with bicalutamide 50 mg as anti-androgen flare protection was initiated on day 0 and this treatment continued for 17 days. On day 3, the first goserelin implant (3.6 mg) was administered and the second and third doses were given on days 31 and 59, respectively.

Baseline Parameters

Baseline parameters included demographic data, medical history, medications, vital signs, electrocardiography, the Eastern Cooperative Oncology Group performance score and history of prostate cancer. Blood and urine were also collected to establish baseline values for assessing the changes in efficacy and safety parameters.

Efficacy Assessments

TPV was assessed by transrectal ultrasound using adequate, well-maintained locally available equipment. A user manual for standardised transrectal ultrasound measurements was provided to all sites. Follow-up measurements for each study participant were carried out using the same equipment. The severity of LUTS and changes during therapy were assessed by the International Prostate Symptom Score (IPSS) questionnaire [12]. The IPSS was recorded before dosing at baseline and at week 4, 8, and 12. Mild, moderate, and severe LUTS were defined as an IPSS of 1–7, 8–19 and 20–35, respectively [13]. LUTS relief was also stratified for patients with a baseline IPSS $\geq$13 [14]. A clinically