available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

A Phase 3, Double-blind, Randomised, Parallel-group, Placebo-controlled Study of Oral Weekly Alendronate for the Prevention of Androgen Deprivation Bone Loss in Nonmetastatic Prostate Cancer: The Cancer and Osteoporosis Research with Alendronate and Leuprolide (CORAL) Study

Laurence H. Klotz [a,*], *Irene Y. McNeill* [a], *Marlene Kebabdjian* [a], *Liying Zhang* [a], *Joseph L. Chin* [b], *Canadian Urology Research Consortium*

[a] *Sunnybrook Health Sciences Centre, 2075 Bayview Ave. #MG408, Toronto, Ontario M4N 3M5, Canada;* [b] *London Health Sciences Centre, 800 Commissioners' Road East, London, Ontario N6A 4G5, Canada*

Article info

Article history:
Accepted September 3, 2012
Published online ahead of print on September 11, 2012

Keywords:
Prostate cancer
Bisphosphonates
Androgen deprivation therapy
Bone mineral density
Bone health

Abstract

Background: Androgen-deprivation therapy (ADT) induces loss of bone mineral density (BMD) and increases the risk of fractures in patients with prostate cancer (PCa). We sought to determine whether a weekly dose of alendronate, an oral bisphosphonate, could reduce this unwanted side-effect.
Objective: To assess whether once-weekly oral alendronate therapy would maintain or improve BMD in men initiating ADT for localised PCa.
Design, setting, and participants: A multicentre, double-blind, randomised, placebo-controlled study, we included hormonally naïve PCa patients initiating ADT with leuprolide acetate 30 mg intramuscularly every 4 mo.
Intervention: Patients were randomised to receive either oral alendronate 70 mg once weekly or placebo for 1 yr. Both groups received daily calcium 1 g and vitamin D 400 international units.
Outcome measurements and statistical analysis: Changes in BMD (at the lumbar spine [LS] and total hip [TH]) and bone markers.
Results and limitations: One hundred ninety-one subjects were enrolled, and 186 were randomised between alendronate ($n = 84$) and placebo ($n = 102$). The alendronate group demonstrated a mean spine BMD increase of 1.7% compared with −1.9% in the placebo group ($p < 0.0001$). Alendronate also increased the BMD at the hip (percent change: 0.7%) compared to placebo (−1.6%). Median urinary N-terminal crosslinking telopeptide of type I collagen (Ntx) values decreased by 3.5% in the alendronate group and increased by 16.5% in the placebo arm, even after adjusting for centre ($p = 0.510$) and baseline urinary Ntx ($p < 0.0001$). Bone-specific alkaline phosphatase (BSAP) decreased a median of 2.25% in the alendronate group and increased a median of 3.12% in the placebo arm, regardless of centre or baseline BSAP or other covariates ($p < 0.0001$). The safety and tolerability profile was similar for the two treatment groups.
Conclusions: Although the study was closed early because of slow accrual, it showed that weekly oral alendronate prevented bone loss and increased bone mass in addition to decreasing bone turnover in patients initiating ADT for localised PCa, with few related side-effects.

* Corresponding author. Tel. +1 416 480 4673; Fax: +1 416 480 6121.
E-mail address: laurence.klotz@sunnybrook.ca (L.H. Klotz).

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2012.09.007

1. Introduction

Androgen-deprivation therapy (ADT) in men is associated with bone loss and an increased risk for fractures [1–11]. Men with prostate cancer (PCa) receiving ADT have increased loss of bone density at multiple skeletal sites [6–12]. Bone loss is maximal in the first year after initiation of ADT [11]. An inference is that therapy to prevent bone loss should be initiated early.

Men initiating ADT are at risk for clinically important loss of bone mineral density (BMD) and osteoporotic fractures. The majority of men do not receive any treatment for this side-effect [13]. Calcium and vitamin D supplementation are recommended, although there is little clinical support for this therapy in the setting of ADT. Calcium and vitamin D have been reported to increase BMD by 0.5–2% over 2–3 yr in a randomised study in men and women with osteoporosis [14]. Previous studies [15–18] have demonstrated that intravenous (IV) bisphosphonate therapy (pamidronate or zoledronic acid) maintains or improves bone mass in men treated with ADT. One randomised study (112 subjects) examined whether once-weekly oral bisphosphonate therapy can maintain or improve bone mass in these patients and showed benefit [19,20]. Treatment with weekly alendronate has also been reported to reduce BMD loss in osteoporotic patients with PCa on ADT [21]. More recently, denosumab, a monoclonal antibody directed against receptor activator of nuclear factor-κB ligand (RANKL), has been shown to improve BMD in PCa patients undergoing ADT [22].

After this study was initiated and accruing patients, a similar although smaller randomised study of alendronate in men on ADT was published [19]. Given the clinical importance of the loss of BMD in men on ADT, we elected to continue the study.

2. Methods

The objective of this study was to determine whether once-weekly oral alendronate would maintain or improve BMD in men receiving ADT. The primary outcome was the percentage change in spine BMD after 12 mo of therapy. Secondary outcomes included percentage change in total hip (TH) BMD; changes in bone markers of resorption and formation; and the predictive value of other factors, including age, body mass index (BMI), alcohol intake, previous history of hypogonadism, baseline BMD, prevalent vertebral and nonvertebral fractures, family history of osteoporotic fractures, and the safety and tolerability of alendronate.

This multicentre, double-blind, randomised, placebo-controlled study was carried out in 30 Canadian urology sites. Eligible subjects were men with histologically confirmed PCa in whom $\geq$1 yr of ADT was indicated because of prostate-specific antigen (PSA) failure. Prior ADT was permitted as long as it had been discontinued at least 1 yr prior to study entry. Treatment with an antiandrogen for up to 30 d prior to initiation of luteinising hormone-releasing hormone (LHRH) therapy was also permitted and could be continued for the duration of the study at the investigator's discretion. Exclusion criteria were hypocalcaemia, estimated glomerular filtration rate $<$35 ml/min, liver function tests $>$1.5 times the upper limit of normal, a history of metabolic bone disease, bilateral hip replacement, prior treatment with a bisphosphonate medication or therapy with glucocorticoids for $>$3 mo prior to enrolment, and any contraindications for oral bisphosphonate therapy. Patients were staged with bone scan only. Men with metastatic PCa or any non-PCa diagnosed within the past 5 yr were excluded. Written informed consent was obtained from all subjects. Approval was obtained from each participating institution's research ethics board.

Subjects initiated ADT with leuprolide acetate 30 mg intramuscularly every 4 mo and were randomised to receive either oral alendronate 70 mg once weekly or placebo for 1 yr. All subjects self-administered oral daily calcium (equivalent to 500 mg elemental calcium) and vitamin D (400 international units [IU]). Calcium and vitamin D use prior to randomisation was not assessed. A randomisation schedule was generated linking sequential numbers to treatment codes allocated at random on a one-to-one basis. Sites received study drug in blocks of four numbered kits containing either alendronate or placebo, although allocation between alendronate and placebo was not necessarily balanced in each block of four. Subjects were randomised to the next kit number at the site in the order in which they qualified from the screening phase for study inclusion.

At screening, subjects were questioned regarding family history of osteoporotic fractures, caffeine and alcohol intake, smoking history, and fracture history. Subjects were also interviewed on their level of physical activity by responding to questions on the type (light, moderate, or vigorous) and amount (quantified in 30-min increments) on average per week at each visit. Routine haematology, total serum calcium, phosphorus, PSA, and testosterone and parathyroid levels were assayed every 4 mo by the site's local laboratory. Markers of bone resorption (urinary N-terminal crosslinking telopeptide of type I collagen [Ntx]) and formation (bone-specific alkaline phosphatase [BSAP]) were also collected every 4 mo. BMD at the lumbar spine (LS) and TH was determined by dual energy x-ray absorptiometry (DEXA) scan prior to initiation of study therapy and at the end of the 12-mo study period. Concomitant medications and adverse events were recorded throughout the trial.

Patient and biochemical characteristics for the intent-to-treat (ITT) population were summarised. Results were expressed as mean, standard deviation (SD), median, and interquartile range (IQR) for demographics and BMD variables. To compare demographics, an analysis of variance (ANOVA) model with treatment and centre as fixed effects was performed. The response variable was demographics (ie, age, number of years smoking), and the independent variables were treatment (A = alendronate; B = placebo) and study centre (16 centres). Analysis of covariance (ANCOVA) was used to analyse the primary and secondary efficacy variables, with treatment and centre as fixed effects. Baseline BMD value and other demographics were considered covariates. Subjects within each centre were considered as random effects. The χ^2 test was also applied to the physical activities (type and level) at month 4, month 8, and end of study. All calculations were conducted using SAS version 9.2 software (SAS Institute, Cary, NC, USA). The PROC MIXED procedure in SAS was used for ANOVA and ANCOVA modelling.

Loss of BMD has been clearly established as correlating with fracture risk [23]. This study incorporated the surrogate end point of BMD loss at the end of 1 yr as a primary end point rather than fracture reduction. This was done to achieve a manageable cohort size and required length of follow-up relative to the resources available for the study.

An original sample size of 216 (108 per group) was calculated, assuming a treatment difference of 2.0% in the mean percent change from baseline in LS BMD at 12 mo between the two groups, an SD of 4.5%, 90% power, and a two-sided type I probability of 0.05. The difference of 2.0% was based on the administration of vitamin D and calcium in the placebo arm, for which a change of 1% was expected.

Subjects were followed for 1 yr. Accrual was anticipated to require 18 mo in about 30 Canadian centres. However, because of slow accrual, the study was closed with 191 subjects accrued in a 28-mo period.