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Research Article

# Prevention of aromatase inhibitor-induced bone loss with alendronate in postmenopausal women: The BATMAN Trial

Anna J. Lomax [a,*], Saw Yee Yap [a], Karen White [a,b], Jane Beith [c], Ehtesham Abdi [d,e], Adam Broad [a,b], Sanjeev Sewak [a], Chooi Lee [a], Philip Sambrook [f,g], Nicholas Pocock [h], Margaret J. Henry [i,j], Elaine G. Yeow [a], Richard Bell [a]

[a] Andrew Love Cancer Centre, The Geelong Hospital, Victoria, Australia
[b] St John of God Geelong Hospital, Victoria, Australia
[c] Royal Prince Alfred Hospital, New South Wales, Australia
[d] Tweed Hospital, New South Wales, Australia
[e] Griffith University, Gold Coast, Australia
[f] Royal North Shore Hospital, New South Wales, Australia
[g] University of Sydney, New South Wales, Australia
[h] St Vincent's Hospital, New South Wales, Australia
[i] Barwon South Western Region Integrated Cancer Services, Victoria, Australia
[j] Department of Medicine, Deakin University, Victoria, Australia

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ABSTRACT

Postmenopausal women on aromatase inhibitors (AI) are at risk of aromatase inhibitor-associated bone loss (AIBL) and fractures.

In 2005 Osteoporosis Australia proposed an algorithm for bisphosphonate intervention. Three hundred and three postmenopausal women with early breast cancer (EBC) were enrolled (osteoporotic, $n=25$; osteopaenic, $n=146$; normal bone mineral density (BMD), $n=126$). Weekly alendronate (70 mg) treatment efficacy as triggered by the algorithm in preventing bone loss was evaluated. All patients received anastrozole (1 mg daily), calcium and vitamin D.

*Results:* All osteoporotic patients received alendronate at baseline. Eleven out of the 146 (7.5%) osteopaenic patients commenced alendronate within 18 months of participation and eleven commenced after. One hundred and twenty four out of the 146 (84.9%) osteopaenic patients and all 126 with normal baseline BMD did not trigger the algorithm.

At three years, lumbar spine mean BMD increased (15.6%, $p<0.01$) in the osteoporotic group. BMD in the osteopaenic group with early intervention significantly increased at three years (6.3%, $p=0.02$). No significant change was seen in the late intervention group. No change was observed in those with osteopaenia without alendronate.

There was a significant drop in lumbar spine (−5.4%) and hip (−4.5%) mean BMD, in the normal BMD group, none of whom received alendronate.

Fracture data will be presented.

*Conclusion:* In postmenopausal women with endocrine-responsive EBC, BMD improved over time when a bisphosphonate is administered with anastrozole in osteoporotic patients using an osteoporosis schedule. Subjects with normal baseline BMD experienced the greatest BMD loss, although none became osteoporotic.



## 1. Introduction

The cancer survival rates in Australia from 1998 to 2004 indicates that the majority of women diagnosed with breast cancer will survive over the long term with 88.0% alive at five years and 79.4% at ten years [1]. Extended survival exposes the majority of patients to the late effects of breast cancer therapies. Osteoporosis and the increased risk of associated skeletal related events are recognised as undesirable outcomes of various adjuvant therapies for early breast cancer [2]. Surveillance strategies for breast cancer need to incorporate monitoring for recurrence of disease as well as strategies to prevent and manage the bone related complications of adjuvant therapies.

Aromatase inhibitors in early breast cancer have demonstrated greater efficacy compared to tamoxifen in postmenopausal women with improved disease free survival, time to recurrence and time

* Corresponding author.
*E-mail address:* annalomax@y7mail.com (A.J. Lomax).

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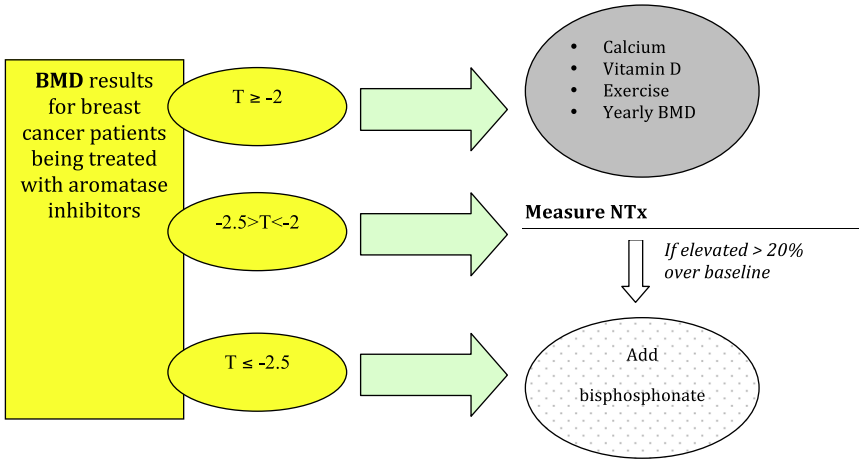


**Fig. 1.** Osteoporosis Australia bone maintenance algorithm, using T-score bone mineral density changes and urine Ntx elevation to guide bisphosphonate management.

to distant recurrence [3]. The suppression of oestrogen levels with AIs results in accelerated bone mineral loss and increased fracture risk. AIBL almost doubles the rate of loss seen in healthy postmenopausal women [4]. Results from the ATAC sub-study demonstrated that progressive AIBL occurs throughout the duration of AI treatment. This is greater in the lumbar spine in the first two years of therapy commencement and the decline appears to be less marked in years two to five of treatment but does not slow down in the hip [5].

In 2005, Osteoporosis Australia proposed an algorithm [6] to manage AIBL (Fig. 1). The algorithm assesses changes in bone mineral density (BMD) and N-telopeptide (NTx, a bone resorption marker) to determine timing of bisphosphonate therapy commencement. The Bisphosphonate and Anastrozole Trial – Bone Maintenance Algorithm Assessment (BATMAN) was designed to test the utility of this algorithm in postmenopausal women with hormone-receptor positive early breast cancer receiving adjuvant anastrozole, and the efficacy of intervention with alendronate, given in an osteoporosis schedule. Most studies in this area have excluded patients with osteoporosis due to the concern of worsening BMD. This study specifically addresses the issues of women with osteopaenia and osteoporosis in this setting.

## 2. Patients and method

Eligible participants were postmenopausal women with Stage I–IIIa hormone receptor positive breast cancer assessed as suitable for treatment with an aromatase inhibitor, specifically anastrozole. Postmenopausal status was defined as age $>55$ years with cessation of menstruation; $<55$ years of age and no menses for 12 months; $>$ 50 but $<55$ and amenorrhoeic (spontaneous, hysterectomy) and with postmenopausal gonadotrophin or oestradiol levels (luteinising hormone $>14$ IU/L, follicle stimulating hormone levels $>40$ IU/L, oestradiol $<110$ pmol/L or according to the reference range for the laboratory involved); or bilateral oophorectomy. Following the observation of resumption of menses and reversal of menopause in a number of patients all of whom were under 50 years of age, we amended the entry criterion to exclude women under 50 years. Hormone replacement therapy must have been discontinued at least 2 weeks prior to registration. Other eligibility requirements were WHO performance status $\leq 2$, with adequate renal and liver function.

Patients receiving prior treatments with bisphosphonates and continuous systemic corticosteroids within the past 12 months were excluded. Any prior use of parathyroid hormone (PTH) for more than 1 week; systemic sodium fluoride for $>3$ months during the past 2 years; any drugs known to affect the skeleton (eg. calcitonin, mithramycin, or gallium nitrate) were not allowed prior to and during the study. Patients with history of diseases with influence on bone metabolism (e.g. Paget's disease, Osteogenesis Imperfecta, and primary or secondary hyperthyroidism), lactose intolerance, delayed oesophageal emptying; previous or concomitant malignancy within the past 5 years, were also excluded. Patients with a fracture due to minimal trauma that was detected on baseline radiology were excluded from the study.

Written informed consent was obtained from each patient before inclusion. The study was approved by the Barwon Health Human Research Ethics Committee (HREC), Eastern Health HREC, St Vincent's HREC, North Coast Area Health Service HREC, and Sydney South West Area Health Service HREC. Eight Australian oncology centres participated. These centres included Barwon Health, St John of God Healthcare Geelong, South West Healthcare (Warrnambool), Box Hill Hospital, Maroondah Hospital, St. Vincent's Hospital Melbourne, Tweed Hospital and Royal Prince Alfred Hospital.

The study was conducted in accordance with the National Health and Medical Research Council's National Statement on Ethical Conduct in Research Involving Humans (June 1999) and the CPMP/ICH Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

Osteoporosis was defined as BMD 2.5 standard deviations or more below the reference range mean for young adults. Osteopaenia being those with a BMD between 1 and 2.5 standard deviations below the young adult mean [7]. Lumbar spine (L2-L4) and femoral neck BMD was quantified with Lunar DPX-L (Lunar, Madison, WI, USA), GE-Lunar Prodigy (Prodigy; GE Lunar, Madison, WI, USA) or Norland Excell™ machines. Dual-energy X-ray absorptiometry (DXA) at baseline, 1, 2 and 3 years assessed using Norland machines were converted to Lunar equivalents using the Genant conversion equations [8]. N-telopeptide (NTx) is a marker of bone resorption. Urine samples for urinary N-telopeptide (uNTx) were collected at baseline, and at 6 months after registration. Participants requiring alendronate were retested 6 months after commencing alendronate.

All patients were commenced on oral anastrozole 1 mg daily, calcium ($\geq$ 500 mg per day) and Vitamin D ($\geq$ 400 IU daily) supplements. No dose modifications were permitted for the duration of the study for those receiving either anastrozole or alendronate.

In accordance with the OAA, patients with a BMD T-Score below $-2.5$ S.D. at either the lumbar vertebra or femoral neck at