Journal of Steroid Biochemistry & Molecular Biology 125 (2011) 112–119

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

# Bone metabolism and quality-of-life of postmenopausal women with invasive breast cancer receiving neoadjuvant hormonal therapy: Sub-analyses from celecoxib anti-aromatase neoadjuvant (CAAN) trial

Louis W.C. Chow[a,b,c,*], Adrian Y.S. Yip[b], W.P. Chu[b], Wings T.Y. Loo[b,c], Masakazu Toi[b,d]

[a] Clinical Trials Centre, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[b] Organisation for Oncology and Translational Research, Hong Kong
[c] UNIMED Medical Institute, Hong Kong
[d] Department of Surgery, Kyoto University, Japan

ARTICLE INFO

*Article history:*
Received 30 April 2010
Received in revised form
28 December 2010
Accepted 31 December 2010

*Keywords:*
Breast cancer
Neoadjuvant
Aromatase inhibitor
Cyclooxygenase-2 inhibitors
Bone metabolism
Quality-of-life

ABSTRACT

*Objective:* Anti-aromatase therapy is important in the treatment of breast cancer in postmenopausal women but they have effects on the bone mineral density (BMD) and osteoporosis. Cyclooxygenase-2 (COX-2) inhibitors have been shown to be effective in chemoprevention in animal and clinical studies. A proof of principle study was performed to investigate the efficacy of combing anti-aromatase therapy (exemestane) and COX-2 inhibitors neoadjuvantly. The changes in the BMD, bone turnover proteins and quality-of-life (QoL) were analyzed and presented here.

*Method:* 82 postmenopausal patients with histologically confirmed invasive hormone-sensitive breast cancers were included for the neoadjuvant therapy (NHT). 30 patients received exemestane (EXE) 25 mg daily and celecoxib (CXB) 400 mg twice daily (group A), 24 patients received EXE 25 mg daily (group B) and 28 patients received letrozole (LET) 2.5 mg daily (group C). The same assigned treatment was intended to continue for 2 years to study the changes in the bone metabolism. BMD of 48 patients were analyzed; 23 belongs to group A, 10 to group B and 15 to group C. The serum bone turnover proteins bone-specific alkaline phosphatase (BAP) and carboxyterminal crosslinked telopeptide of type I collagen (ICTP), were measured with commercially available test kits before treatment, 3 months and 15 months after treatment. Functional Assessment of Cancer Therapy core questionnaire (FACT-G) with its additional breast cancer subscale were performed at baseline, 4, 8, and 12 weeks after NHT.

*Result:* Difference between groups ($p = 0.007$) for BMD at femur was significant. The changes of BMD in group B patients were significantly greater than patients in group A ($p = 0.011$, CI = 0.063–0.437), and group C ($p = 0.003$, CI = 0.146–0.620). The mean BAP increased from baseline in group B patients but decreased from baseline in group C patients at 3 months and 15 months. No statistical significance was found in the FACT-G scores and FACT-B scores among different groups at baseline, week 4, week 8 and week 12 after NHT. The Breast Cancer Subscale scores in group A patients were significantly higher than that of group C patients ($p = 0.021$). After 4 weeks of NHT, negative changes of FACT-B and FACT-G scores were found in group B and C patients, but there were positive changes in group A patients. Significant differences of FACT-B score ($p = 0.008$) and FACT-G score ($p = 0.019$) were observed at that time point.

Article from the Special issue on Targeted Inhibhitors.



## 1. Introduction

Breast cancer is the most common cancer among women worldwide, which accounts for about 26% of all female cancers [1,2]. The global cancer incidence was estimated at 1.15 million new cases in 2002 [1]. Regular and early screening and therapeutic developments have played an important role in increasing the survival rate, and that more patients are now receiving long-term adjuvant treatments.

Many breast cancer cases are associated with female hormones exposure and the relationship between hormone and breast cancer

*Abbreviations:* PWB, physical well-being; SWB, social well-being; EWB, emotional well-being; FWB, functional well-being; BCS, breast cancer subscale; SD, standard deviation.

* Corresponding author at: Organisation for Oncology and Translational Research, Unit A, 9/F., CNT Commercial Bldg., 302 Queen's Road Central, Hong Kong. Tel.: +852 2117 8011; fax: +852 2117 0021.
*E-mail addresses:* lwcchow@ootr.org, lwcchow@hkucc.hku.hk (L.W.C. Chow).

0960-0760/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jsbmb.2010.12.018

has been discussed since 1896 [3]. Menarche at an early age and a late menopause may increase the breast cancer risk, while an early menopause may decrease the risk [4–6]. The breast epithelium proliferation due to the hormone fluctuations has been associated with increased chances of cancer initiation [7]. Our previous study showed that about 55% of patients possessed hormonal receptors and the frequency of hormonal receptor positivity increased with advancing age [8]. These suggest that the steroid receptor plays an important role in breast tumorigenesis and that tumor cells and normal breast cells may have different steroid receptor signaling. It is therefore of interest for researchers to investigate the effectiveness of steroid inhibitors on breast cancer.

Aromatase is an enzyme complex which belongs to the cytochrome P450 (CYP) 19 family [9–11]. It is expressed in many human tissues, but its level is highest in ovaries of premenopausal women, and in the peripheral adipose tissues of postmenopausal women [12–14]. Aromatase converts androgen into estrogen, which then circulates and binds to the estrogen receptor (ER), by which they promote the growth of epithelial cells. The ERs then bind to gene promoters in the nucleus, thus activating cell division and inhibit apoptosis. In premenopausal women, most of the estrogen is produced in the ovaries and are sensitive to luteinizing hormone (LH) changes; however, in postmenopausal women, most estrogen is produced from the conversion of androgens in peripheral tissue [15]. Therefore, the inhibition of the ER expression has become a useful target in estrogen-dependent diseases, such as breast cancer.

The role of aminoglutethimide [16], a non-selective inhibitor blocking the cholesterol side-chain cleavage enzymes and C-21, C-11, and C-18 steroid hydroxylases [17,18], is able to reduce estrogen production by over 90% [19,20]. Its success led to the research and development of the second generation AIs such as formestane and fadrozole with improved potency. However, the dosage was limited by either metabolic or symptomatic side effects, such as fatigue, dizziness, nausea and vomiting. The third generation drugs are therefore further developed to inhibit the activity of aromatase at usable dosages associated with fewer side effects, and with a higher specificity.

The third-generation AIs are classified according to their chemical structures as steroidal (type I inhibitors), for example exemestane; or nonsteroidal (type II inhibitors), such as letrozole and anastrozole. All the AIs block the aromatase activity by inhibiting the estrogen synthesis. But they differ in the aromatase binding mechanism, and the androgenic properties.

The type 1 steroidal AI acts as a competitive inhibitor against androstenedione and as an enzyme inactivator. As enzyme inactivators they function as “suicide inhibitors” in which aromatase converts the AI into a chemically reactive intermediate which can be bound covalently to the substrate binding site of the aromatase. As a result, the enzyme is irreversibly inactivated and the AI inactivator is unable to bind to other enzymes permanently [21]. These AIs have selectivity for the enzyme target. The recovery of enzyme activity is dependent on the enzyme re-synthesis and the drug pharmacokinetics. Therefore, the type I AI has got a long-term effectiveness.

The type II AIs can interact noncovalently with the iron atom of the heme prosthetic group of the enzyme due to the presence of a basic nitrogen atom [22]. They occupy the substrate-binding site of the enzyme and thus prevent the androgen substrate from binding to the catalytic site [23]. But this mechanism is reversible, and the AIs can be competitively displaced by the endogenous substrates. The structural aspects of the drugs determine the inhibition specificity to the aromatase enzyme, thus creating a high-affinity binding and limits the AIs from binding to other enzymes. Many AIs have been developed in the past 20 years, and current researches are now focusing on the use of AIs and the combination with other drugs for better efficacy and tolerability. Despite the fact that the efficacy of AI for the treatment of breast cancer in post-menopausal women has been supported by randomized clinical trials [24,25], these patients may be prone to long-term side effects such as osteoporosis.

Beside aromatase, prostaglandin E2 can stimulate estrogen biosynthesis as well [26]. The cyclooxygenase (COX) enzymes catalyze the conversion of arachidonic acid to prostaglandins. Its inducible isoform, COX-2, which is commonly overexpressed in breast cancer, was found to induce the CYP-19 [26,27]. In addition, its high level was associated with angiogenesis and bone and lymph node metastasis [28–30]. The therapeutic possibilities of COX-2 inhibition has been investigated since epidemiological studies suggested the inverse association between regular intake of nonsteroidal anti-inflammatory drugs (NSAIDs) and the breast cancer risk [31–33]. COX-2 inhibitors were found to be able to inhibit the carcinogenesis of mammary tumors in rodent models [34–37]. Celecoxib (CXB), a promising selective COX-2 inhibitor, demonstrated its chemopreventive ability in rodent models with breast cancer. The combined use of COX-2 inhibitors and AI is being studied and they showed promising results as well [38–42].

Randomized clinical trials have shown the effectiveness of using AIs in breast cancer patients, but these drugs may increase adverse events associated with bone health [43,44]. Breast cancer patients receiving cancer chemotherapy may have a higher bone loss chance and a higher potential risk for developing osteoporosis, especially in postmenopausal women, which is probably due to the decreased estrogen concentration [45–47]; whereas in premenopausal women, premature menopause and bone loss may be induced by ovarian damage by chemotherapy [48]. The rate of treatment-associated bone loss may be higher than that in normal postmenopausal women. Breast cancer patients who receive AIs have an estimated bone loss rate of 2.6% per year [49]; whereas normal women have an estimated annual rate of 2% during the first years of menopause, and about 1% per year afterwards [50]. Osteoporotic patients might suffer from bone fractures, pain, disability and even mortality [51]. Therefore, a better understanding of how these drugs affect bone density is necessary.

The selective estrogen-receptor modulator, tamoxifen (TAM), has been the standard endocrine adjuvant therapy of early breast cancer [52]. It interferes with the estrogen from binding to its receptor. 5 years of adjuvant TAM therapy has been proven as an efficient treatment, it may reduce the disease recurrence by about 50% and mortality by 28% in estrogen-receptor-positive (ER+) tumors [53]. It also has a positive effect on bone health in postmenopausal breast cancer patients. However, the clinical use of TAM against osteoporosis is limited due to its toxicity [54,55]. Although TAM has been the gold standard treatment, it has now been challenged by the AIs which have got fewer side effects. The adverse events experienced by patients receiving TAM such as hot flashes, vaginal bleeding, endometrial cancer, thromboembolic events have been associated with long-term TAM treatment [56–59] and these would be reduced by the substitution of AIs. It is also not recommended to receive TAM therapy beyond 5 years because there is no further benefit [54].

Raloxifene hydrochloride is pharmacologically related to TAM, which has been shown to prevent osteoporosis and breast cancer [60,61]. It is a unique selective estrogen receptor modulator (SERM) due to its role of estrogen antagonist in the uterus [62]. It also has antiresorptive effects on bones but less major adverse events had been found in experimental animals and humans than TAM. In Black et al.’s study, a prevention of bone loss and reduced serum cholesterol had been found in ovariectomized rats after receiving raloxifene [63]. Similar results were also reported in Draper et al.’s study, they found that raloxifene (200 mg/day or 600 mg/day) and

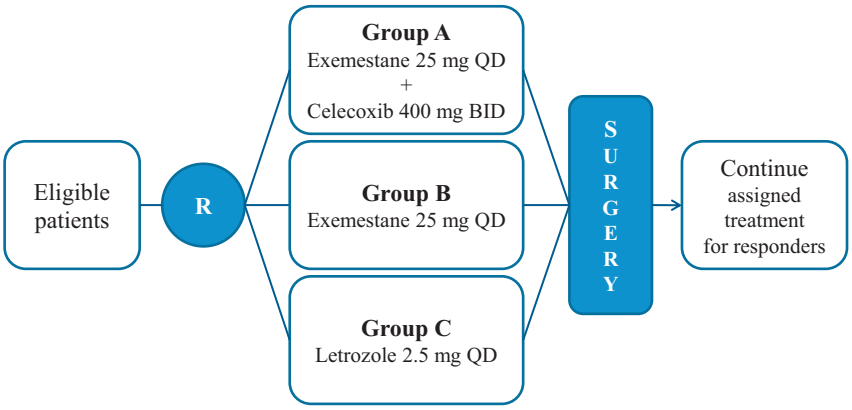


**Fig. 1.** Flow diagram of the process through the phases of the randomized trial. *Abbreviations*: R: randomization; QD: once daily; BID: twice a day.

conjugated equine estrogen both reduced biochemical markers of bone turnover versus placebo [64].

Bone mineral density (BMD), a good indicator of bone loss, is being used to measure the amount of calcium in bone (bone density) and determines the fracture risk. It is strongly recommended for patients especially those with a high risk of getting osteoporosis to determine their BMD before receiving any treatments. BMD is lower in breast cancer patients than normal population group [65] which might be attributed to the long-term estrogen deprivation. While TAM is beneficial on bone health [48], an increased bone loss has been observed with the use of EXE and LET [44,48]. EXE induces bone resorption and formation [66], which increases bone loss at a rate of 2–3% per year [67]. Similarly, LET also has an increased bone loss rate at 2–3% per year [68]. Thus the BMD has to be carefully monitored during the treatment.

Quality-of-life (QoL) is another important key for considering the long-term use of therapy, but is rarely performed in studies of neoadjuvant hormonal therapy (NHT) for breast cancer. This substudy was also conducted to compare the effects of the group taking steroidal AI in combination with COX-2 inhibitor, with the group taking steroidal AI alone, and the group with nonsteroidal AI on changes in BMD, bone turnover proteins and QoL during NHT in postmenopausal women.

## 2. Materials and methods

### 2.1. Patient population

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. All patients were postmenopausal with invasive breast cancer which expressed positive estrogen receptor (ER) and/or progesterone receptor (PgR) status. Other major eligibility criteria included an ECOG performance status $\leq$3 or a Karnofsky performance status $\geq$70, ability of the patient to give written consent and follow instruction well, clinical size of tumor $\geq$3 cm. Exclusion criteria included negative hormonal receptor status, known sensitivity to anti-aromatase drugs or celecoxib, major cardiac disease or LVEF less than 50%, coronary artery disease, active liver disease, renal impairment, and prior history of other malignancy within 5 years of study entry except for basal cell carcinoma or the skin or carcinoma-in situ of the uterine cervix. The nature and purpose of the trial was explained to the patients and informed consent was obtained for inclusion in the trial.

### 2.2. Study design

In this randomized study, patients were randomly assigned to receive EXE 25 mg daily and CXB 400 mg twice a day (group A), EXE 25 mg daily (group B) and LET 2.5 mg daily (group C) for 3 months before surgery. Changes in the bone metabolism were determined as a sub-study in patients responding to the preoperative treatments and receiving the same assigned treatment for at least 2 years after surgery (Fig. 1). Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DEXA) scan at 12 and 24 months after surgery and the serum bone turnover proteins were measured with commercially available test kits before treatment, 3 months and 15 months after treatment.

Assessment of BMD was done by DEXA scan in lumbar spine (L1–L4) and in the femoral neck. BMD's t-score (the standard deviation from the mean value in normal adult) was obtained. To ensure consistency, all DEXA scans were standardized and performed at Hong Kong Sanatorium & Hospital, HKSAR. Assessment of bone metabolism based on measurements of the bone formation marker and bone resportion marker levels in serum: bone-specific alkaline phosphatase (BAP) and carboxyterminal crosslinked telopeptide of type I collagen (ICTP), respectively.

### 2.3. Quality-of-life (QoL)

The Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire has been used to assess the QoL. The FACT-B has 27 questions which measure the general QoL that are associated with cancer; and 9 questions which are breast cancer subscale (BCS). The FACT-G has five subscales assessing physical well being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). 34 out of 79 evaluable patients completed the FACT-G with its BCS at baseline, 4, 8, and 12 weeks after NHT. Incomplete questionnaires were included for cross-sectional analysis. The patients have to indicate how true the statement has been for them during the last 7 days using a five-point scale (from 0 [not at all], 1 [a little bit], 2 [somewhat], 3 [quite a bit], to 4 [very much]). A high score equate with a good QoL, whereas a low score equate with a poorer QoL. Some items have been negatively framed, so they are reversed for further analysis.

### 2.4. Statistical analysis

Parameters were compared using the SPSS for windows release 11.0 (SPSS Inc., USA). One-way ANOVA tests were used to compare means between all groups and post hoc tests were performed to compare means between each group. $p$-Values of less than 0.05 were considered as statistically significant.

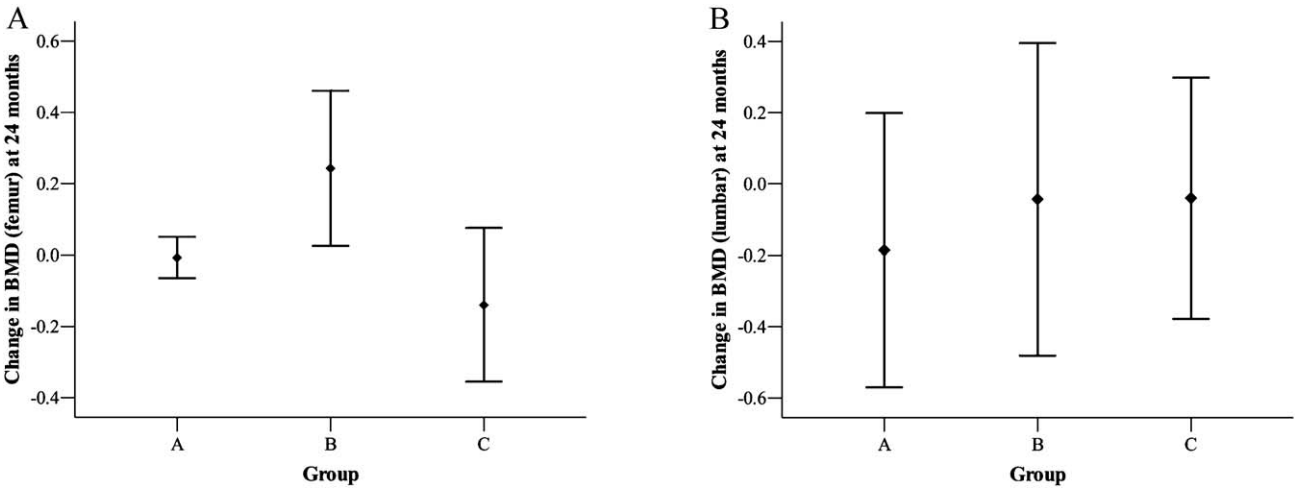


**Fig. 2.** Change in BMD of femur and lumbar spine at 24 months from 12 months after surgery in group A, B and C patients. *Abbreviations*: BMD: bone mineral density

## 3. Results

### 3.1. BMD

Changes in BMD at femur and lumbar were compared at 24 months from 12 months after surgery between groups. A significant difference was observed between groups ($p = 0.007$) for BMD at femur (Fig. 2A), but not significant at spine (Fig. 2B). At 24 months after surgery, there were changes in the BMD at the femur for groups B and C patients, except for group A patients which remained stable. The changes of BMD at femur in group B patients were significantly greater than patients in group A ($p = 0.011$, CI = 0.063–0.437), and group C ($p = 0.003$, CI = 0.146–0.620).

### 3.2. Serum bone turnover proteins

Taking into account of all patients, no significant changes were found in BAP at 3 months (Fig. 3A), and ICTP at 3 and 15 months after the treatment when compared to baseline (Fig. 3B). Although the mean BAP mildly increased from baseline in group B patients but decreased from baseline in group C patients, no significant difference was observed in the percentage change in BAP and ICTP at 3 months and 15 months from baseline between groups.

### 3.3. Quality-of-life (QoL)

No statistical significance was found in the FACT-G scores (PWB, SWB, EWB, and FWB) and FACT-B scores (sum of FACT-G and BCS scores) among different groups at baseline, week 4, week 8 and week 12 after NHT (Table 1). The BCS scores were similar among three groups, but the BCS scores in group A patients were significantly higher than that of group C patients ($p = 0.021$). At 4 weeks after the NHT, the SWB score in group A patients was the highest, whereas group C patients had the lowest score, and the difference was significant ($p = 0.05$). Similarly, there were significant differences in EWB scores ($p = 0.032$) across the three groups after 12 weeks of NHT, however this time group C patients had the highest score, followed by group A patients and group B patients (Table 1). In addition, after 4 weeks of NHT, negative changes of FACT-B (Fig. 4) and FACT-G (Fig. 5) scores were found in group B and C patients, but there were positive changes in group A patients. Significant differences of FACT-B score ($p = 0.008$) and FACT-G score ($p = 0.019$) were observed at that time point.

## 4. Discussion

The survival rate of breast cancer has largely increased due to the improved therapies [69]. A good example is TAM, which has long been the gold standard of treatment against hormone-

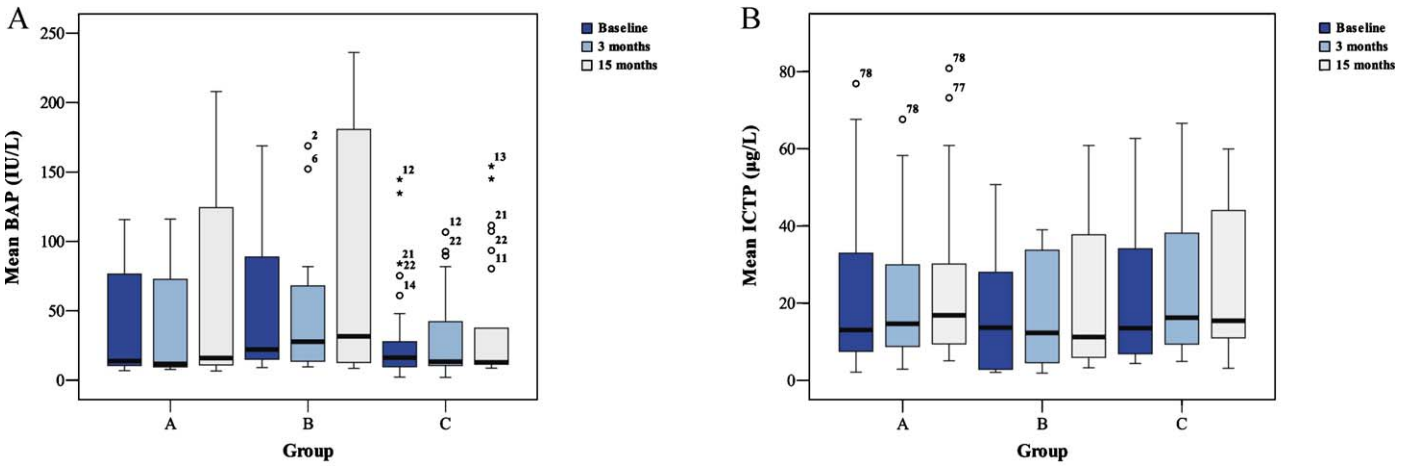


**Fig. 3.** Change in bone turnover proteins BAP (A) and ICTP (B) at baseline, at 3 months, and 15 months after treatment. *Abbreviations*: BAP: bone-specific alkaline phosphatase; ICTP: carboxyterminal crosslinked telopeptide of type I collagen.

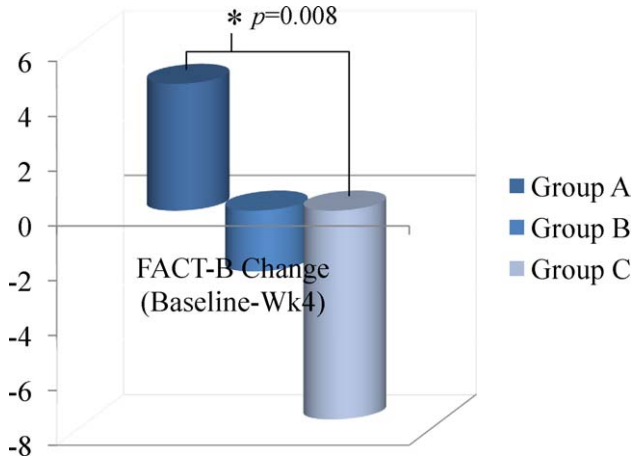


**Fig. 4.** FACT-B score changes in group A, B, and C patients after 4 weeks of neoadjuvant hormonal therapy.

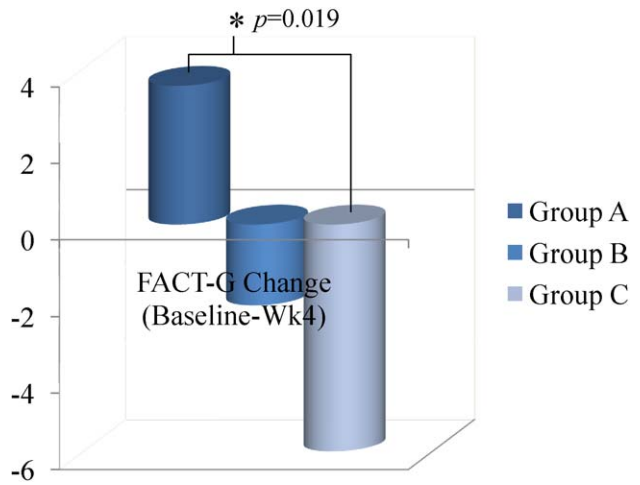


**Fig. 5.** FACT-G score changes in group A, B, and C patients after 4 weeks of neoadjuvant hormonal therapy.

sensitive breast cancer. Unfortunately, drug resistance develops in some tumors [70] leading to the development of AI. Nevertheless, the long-term use of AI might have adverse impact on bone health. Osteoporosis has become an important public health issue in many developed countries. Therefore, people are now more concerned about preventing bone mineral loss and bone fracture. However, it is a complicated disease because many factors are involved and estrogen deficiency may play an important role. The use of AI for treatment of hormone-sensitive breast cancer patients becomes an important clinical issue due to its adverse effect despite its clinical effectiveness.

In postmenopausal women, EXE and LET lower the estrogen levels in serum by 52–72% and 88–98%, respectively [71]. In our study we have found surprising results that the BMD at 24 months and the bone formation protein BAP at 12 months were raised in group B patients who took oral EXE 25 mg daily. This indicates that patients taking EXE might have a lower chance of suffering from osteoporosis or other skeletal problems. A study had found that bone formation markers were significantly but negatively correlated with BMD in femur in placebo group [72]. A preclinical study found that ovariectomised rats had reduced bone formation and resorption markers after taking EXE [73]. Similarly in Coleman et al.'s study, they found that the fracture risk was significantly higher in the patient group taking EXE [74]. However, our results are consistent with Martinetti et al.'s study, which they

**Table 1**
Comparison of mean scores of QoL between groups at baseline, week 4, week 8, and week 12 of neoadjuvant hormonal therapy.

| | Baseline | | Week 4 | | Week 8 | | Week 12 | |
|---|---|---|---|---|---|---|---|---|
| | Mean(SD) | $p^c$ | Mean(SD) | $p^c$ | Mean(SD) | $p^c$ | Mean(SD) | $p^c$ |
| PWB | | | | | | | | |
| A | 24.43(3.34) | | 25.19(2.23) | | 24.19(2.80) | | 24.24(2.40) | |
| B | 24.27(3.24) | | 25.00(2.67) | | 23.89(2.71) | | 23.89(3.37) | |
| C | 26.44(3.39) | 0.122 | 26.15(2.92) | 0.257 | 25.55(3.32) | 0.157 | 25.39(3.73) | 0.320 |
| SWB | | | | | | | | |
| A | 20.13(3.96) | | 20.77(3.59) | | 20.04(3.77) | | 19.88(3.40) | |
| B | 18.57(4.05) | | 19.90(5.05) | | 17.94(6.58) | | 17.67(6.87) | |
| C | 20.19(5.02) | 0.507 | 17.50(8.01) | 0.127 | 19.76(5.34) | 0.388 | 17.17(9.93) | 0.386 |
| EWB | | | | | | | | |
| A | 17.30(3.01) | | 18.30(2.72) | | 18.27(2.81) | | 18.22(2.64) | |
| B | 17.00(5.36) | | 19.05(2.99) | | 19.20(2.73) | | 17.79(1.93) | |
| C | 19.33(3.09) | 0.183 | 19.16(2.51) | 0.470 | 18.75(2.41) | 0.509 | 19.68(1.60) | 0.032* |
| FWB | | | | | | | | |
| A | 21.91(4.18) | | 23.46(4.38) | | 21.42(5.11) | | 21.68(4.43) | |
| B | 20.15(4.97) | | 20.19(7.19) | | 18.44(8.02) | | 19.50(7.25) | |
| C | 22.19(6.22) | 0.512 | 20.58(8.03) | 0.177 | 19.14(6.66) | 0.278 | 17.78(9.63) | 0.209 |
| FACT-G[a] | | | | | | | | |
| A | 83.78(10.59) | | 88.96(9.57) | | 85.00(10.39) | | 84.68(8.77) | |
| B | 81.50(10.18) | | 84.33(13.97) | | 77.80(14.81) | | 78.64(14.85) | |
| C | 87.53(12.56) | 0.362 | 81.43(15.57) | 0.160 | 81.91(8.48) | 0.184 | 81.82(19.37) | 0.483 |
| BCS | | | | | | | | |
| A | 25.30(3.44) | | 26.35(3.05) | | 26.00(2.81) | | 26.80(2.08) | |
| B | 25.08(2.43) | | 25.81(2.42) | | 25.44(2.68) | | 25.33(3.43) | |
| C | 26.81(1.28) | 0.159 | 25.50(3.91) | 0.637 | 25.09(3.93) | 0.614 | 23.89(6.01) | 0.067 |
| FACT-B[b] | | | | | | | | |
| A | 109.09(12.95) | | 115.26(11.29) | | 110.74(11.57) | | 111.32(9.07) | |
| B | 106.00(12.16) | | 110.17(14.33) | | 103.20(14.69) | | 103.36(13.97) | |
| C | 114.40(12.86) | 0.235 | 107.30(16.65) | 0.169 | 106.27(10.96) | 0.191 | 107.91(20.14) | 0.299 |

[a] FACT-G scores equates to the sum of PWB, SWB, EWB and FWB scores.
[b] FACT-B scores equates to the sum of FACT-G and BCS scores.
[c] *p*-Value for difference between groups.
* Statistically significant.

also observed an increase in bone turnover proteins in EXE treatment patient group [75]. And recently Subar et al. suggested that the bone turnover markers in healthy women were increased after taking EXE [76]. Moreover, Goss et al. found that BAP was reduced by 20.1% in patients taking LET [77]. Some other studies also suggested that LET increases bone loss and fracture risk [78–82]. This also indicates that EXE, as a steroidal AI, has got different effect on BMD and bone turnover proteins as no-steroidal LET. However, a study with longer duration and larger sample size is needed to confirm this phenomenon.

In order to explain the difference of AIs, the basic bone physiology has to be understood first. Both androgen and estrogen regulate the normal bone turnover [83]. The importance of estrogen in bone metabolism has been suggested for long; however its underlying mechanism is still not fully understood [84]. Generally, the bone metabolism is regulated by the expression of intracellular and cell surface estrogen receptors by osteoblasts and osteoclasts. Estrogen induces the bone formation activity by osteoblasts. In addition, estrogen reduces bone resorption by decreasing the cytokine production such as interleukin-1 [85]. Besides, estrogen also increases the production of a cytokine called osteoprotegerin, which triggers more osteoclastic apoptosis [86,87]. As a result, estrogen loss increases the bone turnover, which makes the normal bone resorption and formation lose control [84], and eventually causes osteoporosis. The reason which caused the difference on bone loss between EXE and LET could be the different steroidal structure. 17-hydroexemestane, the principal metabolite of EXE plays an important role. It is androgenic, and thus it protects the bone from losing. In contrast, LET is lack of such androgenic activity [88–90]. A previous study showed [67] a possible loss of BMD in patients receiving adjuvant exemestane than that receiving tamoxifen. Patients receiving exemestane had relatively lower mean baseline T-scores of $-0.44 \pm 1.46$ and $-0.48 \pm 1.31$ at spine and hip respectively than those receiving tamoxifen with T-scores of $-0.10 \pm 1.22$ and $-0.23 \pm 1.11$, respectively. The true adverse effect on the change in one-year BMD was barely comparable between groups and that the change indeed did not contribute to osteoporosis. In our study, we did not compare the change in BMD between EXE and tamoxifen, but between different AIs at 24 months from 12 months after surgery and that a positive change in BMD was observed in EXE alone group. The true impact on BMD might be more clearly observed after prolonged adjuvant exemestane.

Apart from the concerned adverse effects of breast cancer therapy, good QoL is also essential for breast cancer patients during and after treatment. In this sub-study, patients receiving exemestane and celecoxib had better QoL as illustrated by positive change in FACT-G and FACT-B scores. The QoL was relatively worsened in patients receiving AI only. Obviously, patients given letrozole suffered from more side effects predominantly by mood alteration, bone and/or muscle aches and hot flashes [38] although, in general, side effects by AI were tolerable. It coincides with relatively worse QoL demonstrated in this sub-study. In view of the positive improvement in QoL in the group with celecoxib, further investigation on the possibility of adding COX-2 inhibitor to AI in adjuvant or neoadjuvant setting is deserved.

Higher level of COX-2 in cancer cells has been associated with poor programmed cell death and was associated with poor prognosis. Therefore, COX-2 has become a therapeutic target. Many studies have been investigating the combination use of chemotherapy drugs and COX-2 inhibitors, and some of them have suggested a better response [91–93]. The efficacy of adding COX-2 inhibitor to AI was comparable to AI alone [38], this sub-study has however demonstrated that patients receiving a combination of EXE and CXB had a better QoL and a stable bone metabolism in general. Therefore, further studies are needed to observe the effect of this combination.

Long-term treatment with AI may have different impacts on BMD, bone turnover proteins and QoL for breast cancer patients. Except BMD, bone turnover proteins have been useful as biochemical markers in assessing metabolic bone diseases. They are relatively safe and cheap than other imaging techniques. They are better in detecting small changes in bone formation and resorption than imaging techniques [94]. Our results have suggested that it is necessary to monitor the bone density in patients over time during the entire treatment, so that treatment against osteoporosis can be done immediately once a reduction in BMD has been detected.

In recent years, estrogen deprivation is regarded as one of chemopreventive strategies for breast cancer. The National Surgical Adjuvant Breast and Bowel Project has launched a clinical trial since 1999 with the use of selective estrogen receptor modulators in a population of health postmenopausal women who are at risk of breast cancer [95,96]. Results are controversial between the use of TAM and raloxifene, but it demonstrated an important milestone for the application of anti-estrogen for breast cancer chemoprevention. As for the use of AI, it is still controversial whether EXE can be used as a preventive agent or not notwithstanding an improvement in BMD. Further investigation is needed to identify the underlying mechanism of how EXE might increase the BMD and bone turnover proteins. It is also notable that patients receiving both EXE and CXB had a relatively stable change in BMD and bone turnover proteins. Although the cardiotoxicity was concerned with the use of NSAID, the combination use of celecoxib and exemestane could be further explored for appropriate dosage and duration in chemoprevention of breast cancer. More studies with larger sample size and longer investigation time can be done to observe the clinical significance of combination use of AI and COX-2 inhibitor.

## 5. Conclusion

Patients receiving both EXE and CXB had a relatively stable change in BMD and bone turnover proteins and relatively better QoL.

## References

[1] D.M. Parkin, F. Bray, J. Ferlay, et al., Global cancer statistics, 2002, CA Cancer J. Clin. 55 (2005) 74–108.
[2] A. Jemal, R. Siegel, E. Ward, T. Murray, J. Xu, C. Smigal, M.J. Thun, Cancer Stat. 56 (2006) 106–130.
[3] A.P. Forrest, Beatson: hormones and the management of breast cancer, J. R. Coll. Surg. Edinb. 27 (1982) 253–263.
[4] M. Lambe, et al., Parity, age at first and last birth, and risk of breast cancer: a population-based study in Sweden, Breast Cancer Res. Treat. 38 (1996) 305–311.
[5] J. Staszewski, Age at menarche and breast cancer, J. Natl. Cancer Inst. 47 (1971) 935–940.
[6] D. Trichopoulos, et al., Menopause and breast cancer risk, J. Natl. Cancer Inst. 48 (1972) 605–613.
[7] S.M. Cohen, L.B. Ellwein, Genetic errors, cell proliferation, and carcinogenesis, Cancer Res. 51 (1991) 6493–6505.
[8] L.W.C. Chow, P. Ho, Hormonal receptor determination of 1052 Chinese breast cancers, J. Surg. Oncol. 75 (2002) 172–175.
[9] E. di Salle, G. Ornati, D. Giudici, et al., Exemestane (FCE 24304), a new steroidal aromatase inhibitor, J. Steroid Biochem. Mol. Biol. 43 (1992) 137–143.
[10] S.R. Johnston, M. Dowsett, Aromatase inhibitors for breast cancer: lessons from the laboratory, Nat. Rev. Cancer 3 (2003) 821–831.
[11] R.W. Brueggemeier, J.C. Hackett, E.S. Diaz-Cruz, Aromatase inhibitors in the treatment of breast cancer, Endocr. Rev. 26 (2005) 331–345.
[12] V.H.T. James, J.M. McNeill, L.C. Lai, C.J. Newton, H. Braunsberg, M. Ghilchik, M.J. Reed, Aromatase activity in normal breast and breast tumor tissues: in vivo and in vitro studies, Steroids 50 (1987) 269–279.
[13] W.R. Miller, P. Mullen, P. Sourdaine, C. Watson, J.M. Dixon, J. Telford, Regulation of aromatase activity within the breast, J. Steroid Biochem. Mol. Biol. 61 (1997) 193–202.
[14] M.J. Reed, The role of aromatase in breast tumors, Breast Cancer Res. Treat. 30 (1994) 7–17.
[15] E.R. Simpson, Sources of estrogen and their importance, J. Steroid Biochem. Mol. Biol. 86 (2003) 225–230.
[16] E.A. Thompson Jr., P.K. Siiteri, Utilization of oxygen and reduced nicotinamide adeninedinucleotide phosphate by human placental microsomes during aromatization of androstenedione, J. Biol. Chem. 249 (1974) 5364–5372.

[17] M.P. Cohen, P.P. Foa, Aminoglutethimide inhibition of adrenal deso lase activity, Proc. Soc. Exp. Biol. Med. 727 (1969) 1086–1090.
[18] S.W.M. Hughes, D.M. Burley, Aminoglutethimide. A "side-effect" turned to therapeutic advantage, Postgrad. Med. J. 46 (1970) 409–416.
[19] P.E. Lonning, Pharmacology of new aromatase inhibitors, Breast 5 (1996) 202–208.
[20] J. Geisler, N. King, G. Anker, et al., In vivo inhibition of aromatization by exemestane, a novel irreversible aromatase inhibitor, in postmenopausal breast cancer patients, Clin. Cancer Res. 4 (1998) 2089–2093.
[21] Y. Hong, B. Yu, M. Sherman, et al., Molecular basis for the aromatization reaction and exemestane-mediated irreversible inhibition of human aromatase, Mol. Endocrinol. 21 (2007) 401–414.
[22] Y.C. Kao, L.L. Cam, C.A. Laughton, D. Zhou, S. Chen, Binding characteristics of seven inhibitors of human aromatase: a site-directed mutagenesis study, Cancer Res. 56 (1996) 3451–3460.
[23] P.A. Cole, C.H. Robinson, Mechanism and inhibition of cytochrome P-450 aromatase, J. Med. Chem. 33 (1990) 2933–2942.
[24] A. Buzdar, A. Howell, Advances in aromatase inhibition: clinical efficacy and tolerability in the treatment of breast cancer, Cancer Lett. 140 (2001), 27-25.
[25] P.E. Goss, K. Strasser, Aromatase inhibitors, J. Clin. Oncol. 19 (2001) 881–894.
[26] Y. Zhao, V. Agarwal, C. Mendelson, E. Simpson, Estrogen biosynthesis proximal to a breast tumor is stimulated by PGE2 via cyclic AMP, leading to activation of promoter II of the CYP19 (aromatase) gene, Endocrinology 137 (1996) 5739–5742.
[27] A. Bennett, E.M. Charlier, A.M. McDonald, J.S. Simpson, I.F. Stamford, T. Zebro, Prostaglandins and breast cancer, Lancet 2 (1977) 624–626.
[28] D.M.A. Watson, R.W. Kelly, R.A. Hawkins, W.R. Miller, Prostaglandins in human mammary cancer, Br. J. Cancer 49 (1984) 459–464.
[29] A. Singhakowinta, H.G. Potter, T.R. Buroker, B. Samal, S.C. Brooks, V.K. Vaitkevicius, Estrogen receptor and natural course of breast cancer, Ann. Surg. 183 (1976) 84.
[30] C. Costa, R. Soares, J.S. Reis-Filho, D. Leitão, I. Amendoeira, F.C. Schmitt, Cyclo-oxygenase 2 expression is associated with angiogenesis and lymph node metastasis in human breast cancer, J. Clin. Pathol. 55 (6) (2002) 429–434.
[31] R.E. Harris, K.K. Namboodiri, W.B. Farrar, Epidemiologic study of non-steroidal anti-inflammatory drugs and breast cancer, Oncol. Rep. 2 (1995) 591–592.
[32] R.E. Harris, K.K. Namboodiri, W.B. Farrar, Nonsteroidal antiinflammatory drugs and breast cancer, Epidemiology 7 (1996) 203–205.
[33] R.E. Harris, S. Kasbari, W.B. Farrar, Prospective study of nonsteroidal drugs and breast cancer, Oncol. Rep. 6 (1999) 71–73.
[34] A.M. Fulton, In vivo effects of indomethacin on the growth of murine mammary tumors, Cancer Res. 44 (1984) 2416–2420.
[35] D.L. McCormick, R.C. Moon, Inhibition of mammary carcinogenesis by flurbiprofen, a non-steroidal anti-inflammatory agent, Br. J. Cancer 48 (1983) 859–861.
[36] P.P. Lee, M.M. Ip, Regulation of proliferation of rat mammary tumor cells by inhibitors of cyclooxygenase and lipoxygenase, Prostag. Leukotr. Essent. Fatty Acids 45 (1992) 21–31.
[37] D.L. McCormick, M.J. Madigan, R.C. Moon, Modulation of rat mammary carcinogenesis by indomethacin, Cancer Res. 45 (1985) 1803–1808.
[38] L.W. Chow, A.Y. Yip, W.T. Loo, C.K. Lam, M. Toi, Celecoxib anti-aromatase neoadjuvant (CAAN) trial for locally advanced breast cancer, J. Steroid Biochem. Mol. Biol. 111 (1–2) (2008) 13–17.
[39] H.F. Kang, X.J. Wang, X.X. Liu, Z.J. Dai, F.J. Xue, X.H. Xue, Chemopreventive effect of tamoxifen combined with celecoxib on DMBA-induced breast cancer in rats, Ai Zheng 25 (11) (2006) 1346–1350.
[40] S. Woditschka, J.D. Haag, B. Mau, R.A. Lubet, M.N. Gould, Chemopreventive effects of celecoxib are limited to hormonally responsive mammary carcinomas in the neu-induced retroviral rat model, Breast Cancer Res. 10 (1) (2008) R18.
[41] P.A. Canney, M.A. Machin, J. Curto, A feasibility study of the efficacy and tolerability of the combination of exemestane with the COX-2 inhibitor celecoxib in postmenopausal patients with advanced breast cancer, Eur. J. Cancer 41 (2006) 2751–2756.
[42] L.Y. Dirix, J. Ignacio, S. Nag, et al., Treatment of advanced hormone-sensitive breast cancer in postmenopausal women with exemestane alone or in combination with celecoxib, J. Clin. Oncol. 26 (2008) 1253–1259.
[43] C. Osborne, D. Tripathy, Aromatase inhibitors: rationale and use in breast cancer, Annu. Rev. Med. 56 (2005) 103–116.
[44] B.A. Mincey, E.A. Perez, Aromatase inhibitors and bone health, in: ASCO 2005 Education Book, 41st Annual Meeting, Orlando, FL, 2005, pp. 27–34.
[45] J. Pfeilschifter, I.J. Diel, Osteoporosis due to cancer treatment: pathogenesis and management, J. Clin. Oncol. 18 (2000) 1570–1593.
[46] B.A. Mincey, Osteoporosis in women with breast cancer, Curr. Oncol. Rep. 5 (2003) 53–57.
[47] J.R. Mackey, A.A. Joy, Skeletal health in postmenopausal survivors of early breast cancer, Int. J. Cancer 114 (2005) 1010–1015.
[48] J. Lester, D. Dodwell, E. McCloskey, et al., The causes and treatment of bone loss associated with carcinoma of the breast, Cancer Treat. Rev. 31 (2005) 115–142.
[49] R. Eastell, R.A. Hannon, J. Cuzick, et al., Effect of anastrozole on bone density and bone turnover: Results of the 'Arimidex' (anastrozole), Tamoxifen, Alone or in Combination (ATAC) Study (abstract 1170), J. Bone Miner. Res. 17 (Suppl. 1) (2002) S165.
[50] J.A. Kanis, Pathogenesis of Osteoporosis and Fracture, Osteoporosis, Blackwell Healthcare Communications, London, 1996, pp. 22–55.
[51] M.S. Aapro, Long-term implications of bone loss in breast cancer, Breast 13 (Suppl. 1) (2004) S29–S37.
[52] M. Candelaria, R. Hurtado-Monroy, P. Vargas-Viveros, S. Carrillo-Muñnoz, A. Duenas-Gonzalez, Tamoxifen-associated vasculitis in a breast cancer patient, World J. Surg. Oncol. 5 (2007) 9.
[53] Early Breast Cancer Trialists' Collaborative Group, Tamoxifen for early breast cancer: an overview of the randomised trials, Lancet 351 (1998) 1451–1467.
[54] B. Fisher, J. Dignam, J. Bryant, et al., Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial, J. Natl. Cancer Inst. 93 (2001) 684–690.
[55] S. Demissie, R.A. Silliman, T.L. Lash, Adjuvant tamoxifen: predictors of use, side effects, and discontinuation in older woman, J. Clin. Oncol. 19 (2001) 322–328.
[56] B. Fisher, J.P. Costantino, D.L. Wickerham, et al., Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study, J. Natl. Cancer Inst. 90 (1998) 1371–1388.
[57] A. Howell, J. Cuzick, M. Baum, et al., Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years adjuvant treatment for breast cancer, Lancet 365 (2005) 60–62.
[58] J. Cuzick, T. Powles, U. Veronesi, et al., Overview of the main outcomes in breast-cancer prevention trials, Lancet 361 (2003) 296–300.
[59] S. Duffy, Gynecological adverse events including hysterectomy occur less frequently with anastrozole than with tamoxifen: data from the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial, J. Clin. Oncol. 23 (16 Suppl.) (2005) 721a.
[60] B. Ettinger, et al., Reduction of Vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene, JAMA 287 (7) (1999) 637–645.
[61] S.R. Cummings, et al., The effect of raloxifene on risk of breast cancer in postmenopausal women, JAMA 281 (23) (1999) 2189–2197.
[62] H.U. Bryant, P.K. Wilson, M.D. Adrian, H.W. Cole, D.L. Phillips, J.A. Doge, T.A. Grese, J.P. Sluka, A.L. Glasebrook, J. Soc. Gynecol. Invest. 3 (1996) 152.
[63] L.J. Black, M. Sato, E.R. Rowley, D.E. Magee, A. Bekele, D.C. Williams, G.J. Cullinan, R. Bendele, R.F. Kauffman, W.R. Bensch, C.A. Frolik, J.D. Termine, H.U. Bryant, Raloxifene (LY139481 HCI) prevents bone loss and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats, J. Clin. Invest. 93 (1994) 63–69.
[64] M.W. Draper, D.E. Flowers, W.J. Huster, J.A. Neild, K.D. Harper, C. Arnaud, A controlled trial of raloxifene (LY139481) HCl: impact on bone turnover and serum lipid profile in healthy postmenopausal women, J. Bone Miner. Res. 11 (1996) 835–842.
[65] J.A. Cauley, F.L. Lucas, L.H. Kuller, M.T. Vogt, W.S. Browner, S.R. Cummings, Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures, JAMA 276 (17) (1996) 1404–1408.
[66] J. Geisler, P.E. Lonning, L.E. Krag, et al., Estrogens and bone metabolism in postmenopausal women with early breast cancer at low risk treated with exemestane: a randomized placebo-controlled study, J. Clin. Oncol. 22 (14 Suppl.) (2004) 531a.
[67] S.E. Jones, J. Cantrell, S. Vukelja, et al., The effect of tamoxifen (T) or exemestane (E) on bone mineral density (BMD) after 1 year of adjuvant treatment of postmenopausal women with early breast cancer, J. Clin. Oncol. 23 (Suppl. 16) (2005) 610a.
[68] E.A. Perez, R.G. Josse, K.I. Pritchard, et al., Effect of letrozole versus placebo on bone mineral density in women completing 5 years of adjuvant tamoxifen: NCIC CTG MA.17b, Breast Cancer Res. Treat. 88 (Suppl. 1) (2004) 404a.
[69] M. Clemons, S. Danson, A. Howell, Tamoxifen ('Nolvadex'): a review, Cancer Treat. Rev. 28 (2002) 165–180.
[70] L.B. Michaud, Adjuvant use of aromatase inhibitors in postmenopausal women with breast cancer, Am. J. Health Syst. Pharm. 62 (2005) 266–273.
[71] A.U. Buzdar, J.F. Robertson, W. Eiermann, J.M. Nabholtz, An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane, Cancer 95 (2002) 2006–2016.
[72] J. Geisler, P.E. Lønning, L.E. Krag, E. Løkkevik, T. Risberg, A.I. Hagen, E. Schlichting, E.A. Lien, E.S. Ofjord, G.E. Eide, A. Polli, E. di Salle, J. Paolini, Changes in bone and lipid metabolism in postmenopausal women with early breast cancer after terminating 2-year treatment with exemestane: a randomised, placebo-controlled study, Eur. J. Cancer. 42 (17) (2006) 2968–2975.
[73] P.E. Goss, S. Qi, A.M. Cheung, H. Hu, M. Mendes, K.P. Pritzker, Effects of the steroidal aromatase inhibitor exemestane and the nonsteroidal aromatase inhibitor letrozole on bone and lipid metabolism in ovariectomized rats, Clin. Cancer Res. 10 (17) (2004) 5717–5723.
[74] R.E. Coleman, L.M. Banks, S.I. Girgis, L.S. Kilburn, E. Vrdoljak, J. Fox, et al., Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study, Lancet Oncol. 8 (2007) 119–127.
[75] A. Martinetti, N. Zilembo, L. Ferrari, G. Massimini, A. Polli, I. La Torre, R. Giovanazzi, P. Pozzi, P. Bidoli, D. De Candis, E. Seregni, E. Bombardieri, E. Bajetta, Bone turnover markers and insulin-like growth factor components in metastatic breast cancer: results from a randomised trial of exemestane vs megestrol acetate, Anticancer Res. 23 (2003) 3485–3491.
[76] M. Subar, P. Goss, T. Thomsen, et al., Effects of steroidal and nonsteroidal aromatase inhibitors (Ais) on markers of bone turnover and lipid metabolism in healthy volunteers, Am. Soc. Clin. Oncol. 23 (2004) 734.

[77] P. Goss, T. Thompsen, J. Banke-Bochita, A randomized, placebo-controlled, explorative study to investigate the effect of low estrogen plasma levels on markers of bone turnover in healthy postmenopausal women during the 12-week treatment with exemestane or letrozole, Breast Cancer Res. Treat. 76 (Suppl 1) (2002) S76 (abstract 267).
[78] P.E. Goss, J.N. Ingle, S. Martino, N.J. Robert, H.B. Muss, M.J. Piccart, et al., A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer, New. Engl. J. Med. 349 (2003) 1793–1802.
[79] E.A. Perez, R.G. Josse, K.I. Pritchard, J.N. Ingle, S. Martino, B.P. Findlay, T.N. Shenkier, R.G. Tozer, M.J. Palmer, L.E. Shepherd, et al., Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17, J. Clin. Oncol. 24 (2006) 3629–3635.
[80] R.E. Coleman, L.M. Banks, E. Hall, D. Price, S. Girgis, J.M. Bliss, R.C. Coombes, Intergroup exemestane study: 1 year results of the bone sub-protocol [abstract 401], Breast Cancer Res. Treat. 88 (2004) S35.
[81] E. McCloskey, R. Hannon, G. Lakner, G. Clack, A. Miyamoto, R. Eastell, The letrozole (L), exemestane (E), and anastrozole (A) pharmacodynamics (LEAP) trial: a direct comparison of bone biochemical measurements between aromatase inhibitors (AIs) in healthy postmenopausal women, J. Clin. Oncol. 24 (2006) 555.
[82] E. McCloskey, Effects of third-generation aromatase inhibitors on bone, Eur. J. Cancer. 42 (2006) 1044–1051.
[83] J.E. Compston, Sex steroids and bone, Physiol. Rev. 81 (2001) 419–447.
[84] B.L. Riggs, S. Khosla, L.J. Melton 3rd, Sex steroids and the construction and conservation of the adult skeleton, Endocr. Rev. 23 (3) (2002) 279–302.
[85] L.C. Hofbauer, M. Schoppet, Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases, JAMA 292 (4) (2004) 490–495.
[86] J. Pfeilschifter, Role of cytokines in postmenopausal bone loss, Curr. Osteoporosis Rep. 1 (2003) 53–58.
[87] M.K. Lindberg, L. Vandenput, S. Moverare Skrtic, D. Vandèrschueren, S. Boonen, R. Bouillon, et al., Androgens and the skeleton, Minerva Endocrinol. 30 (2005) 15–25.
[88] D.C. Johannessen, T. Engan, E. Di Salle, M.G. Zurio, J. Paolini, G. Ornati, G. Piscitelli, S. Kvinnsland, P.E. Lonning, Endocrine and clinical effects of exemestane (PNU 155971), a novel steroidal aromatase inhibitor, in postmenopausal breast cancer patients: a phase I study, Clin. Cancer Res. 3 (1997) 1101–1108.
[89] P.E. Goss, S. Qi, R.G. Josse, K.P. Pritzker, M. Mendes, H. Hu, et al., The steroidal aromatase inhibitors exemestane prevents bone loss in ovariectomized rats, Bone 34 (2004) 384–392.
[90] C.L. Shapiro, et al., Aromatase inhibitors and bone loss: risks in perspective, J. Clin. Oncol. 23 (22) (2005) 4847–4849.
[91] P.A. Canney, A phase II study of the efficacy and tolerability of the combination of exemestane with the cyclooxygenase-2 inhibitor celecoxib in postmenopausal patients with advanced breast cancer, Proc. Am. Soc. Clin. Oncol. 22 (2003) 40 (abstract 158).
[92] L.Y. Dirix, J. Ignacio, S. Nag, Final results from an open-label, multicenter, controlled study of exemestane +/− celecoxib in postmenopausal women with advanced breast cancer (ABC) progressed on tamoxifen (T), Proc. Am. Soc. Clin. Oncol. 22 (2003) 20 (abstract 77).
[93] E. Pesenti, J.L. Masferrer, E. di Salle, Effect of exemestane and celecoxib alone or in combination on DMBA-induced mammary carcinoma in rats, Breast Cancer Res. 69 (2001) 288 (abstract 445).
[94] N. Majkic-Singh, M. Ilic, S. Ignjatovic, G. Aleksandra Postic, Assessment of four biochemical markers of bone metabolism in post-menopausal osteoporosis, Clin. Lab. 48 (2002) 407–413.
[95] D.L. Wickerham, J.P. Costantino, V.G. Vogel, W.M. Cronin, R.S. Cecchini, L.G. Ford, N. Wolmark, The use of tamoxifen and raloxifene for the prevention of breast cancer, Recent Results Cancer Res. 181 (2009) 113–119.
[96] V.G. Vogel, J.P. Costantino, D.L. Wickerham, et al., Update of the national surgical adjuvant breast and bowel project Study of Tamoxifen and Raloxifene (STAR) P-2 trial: preventing breast cancer, Cancer Prev. Res. 3 (2010) 696–706.