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

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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.

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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