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Celecoxib anti-aromatase neoadjuvant (CAAN) trial for locally advanced breast cancer: preliminary report☆

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Abstract

Anti-aromatase therapy is important in the treatment of breast cancer in postmenopausal women. 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 in hormone-sensitive postmenopausal breast cancers. The initial results are reported. The patients were randomly assigned to receive exemestane 25 mg daily and celecoxib 400 mg twice daily (group A), exemestane 25 mg daily (group B) and letrozole 2.5 mg daily (group C). The analysis was based on 20 patients who received at least one cycle of treatment. Fourteen patients completed two cycles and 12 patients three cycles. All groups showed clinical response and there was decrease in tumor area in each group. However, complete clinical response was only observed for group A patients. There was also progressive decline in blood CEA and CA15.3 levels but the differences between the three groups were not significant. The results of the preliminary analysis are encouraging but definitive conclusion could only be drawn after the completion of the study.

Keywords: CAAN; COX-2; Breast cancer

1. Introduction

Breast cancer is the leading cause of death among women between the ages of 30 and 60 years. In the United States, an estimate of about 180,000 new cases of breast cancer are diagnosed each year and roughly 40,000 women will die from it each year. The incidence of breast cancer in Asia is also shown to be increasing recently, especially in the more affluent cities [1]. Breast cancer has become such a major health care issue that researchers and clinicians all over the world have shown great efforts in the past decades to find out a safe, cheap and effective treatment option.

Breast cancer is commonly associated with female hormones exposure. Growth stimulation of human breast cancer by sex hormones has been known for more than 100 years. In fact, Beatson demonstrated that oophorectomy could lead to shrinkage of breast tumors in premenopausal women in 1896 [2]. It is commonly accepted now that most breast cancers are hormone dependent. Our previous study showed that about 55% of patients possessed hormonal receptors and the frequency of hormonal receptor positivity increased with advancing age [3]. This special feature of breast cancer provides an opportunity for researchers to investigate the usefulness of endocrine therapy in the management of breast cancer. Current researchers are focusing their efforts on the use of aromatase inhibitors.

Aromatase is an enzyme complex consisting of a cytochrome P-450 hemoprotein and a flavoprotein. Its function is to convert C-19 androgen, such as testosterone and androstenedione, to C-18 estrogen such as estradiol and estrone. The aromatization of adrenal androgens to estrogen is taking place mostly in the peripheral tissues like fat and muscle. Aromatization could also occur in breast cancers and the activity is mainly happening in the epithelial cells [4].

The cyclooxygenase enzymes are important for the conversion of arachidonic acid to prostaglandins, and their metabolites play a pivotal role in multiple physiologic and pathophysiologic processes. The inducible isoform, COX-2, is commonly over-expressed in breast cancer. Recent work suggests that COX-2-derived metabolites may contribute at multiple points throughout tumorigenesis, including premalignant hyperproliferation, transformation, maintenance of tumor viability, growth, invasion, and metastatic spread. It may also promote tumor-specific angiogenesis, inhibit

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apoptosis and induce proangiogenic factors such as VEGF, inducible nitrogen oxide synthetase (iNOS) promoter, IL-6, IL-8 and TIE-2 [5].

The clinical efficacy and tolerability of anti-aromatase agents have been demonstrated. Recent clinical trials show that these agents, whether type I or II, could improve the objective response (OR) rates by about 3–10% and the median survival by about 3 months for metastatic breast cancer even after tamoxifen failure [6]. Celecoxib (CXB) is a selective cyclooxygenase-2 inhibitor. It has chemopreventive and chemotherapeutic properties in rodent models of breast cancer.

The present trial is a proof of a principle study to evaluate the treatment efficacy of exemestane in combination with CXB in the neoadjuvant setting for postmenopausal hormonal receptor positive patients. As both drugs are well tolerated, most patients would be able to complete the treatment and we would be able to show the objective response rate in a documented fashion.

2. Patients and methods

Local Ethics Committee approval was obtained for this trial. Ninety patients are intended to be recruited. They should be postmenopausal with proven breast cancer. They should have a ECOG performance status of 3 or less of a Karnofsky score of 70 or above. They should be able to give written consent and follow instructions well. The clinical size of the tumor should be 3 cm or greater.

The diagnosis of breast cancer was confirmed by mammographic examinations and cytological examinations of the fine needle aspirates. Routine staging workup, including chest X-rays, ultrasound of the liver and bone scan, was performed. Core biopsy was taken for histological typing as well as determination of the status of the molecular markers and hormonal receptors. If there were no reasons for exclusion (Table 1), the nature and purpose of the trial was explained to the patients and informed consent was obtained for inclusion in the trial.

Blood was drawn from the patients the day before treatment was started and on completion of each cycle of treatment. The blood tumor markers including CEA and CA15.3 were determined.

Table 1
Exclusion criteria

Negative estrogen receptor status
Known sensitivity to anti-aromatase drugs or celecoxib
Major cardiac disease or LVEF <50%
Coronary artery disease
Active liver disease
Renal impairment
Prior history of other malignancy within 5 years of study entry, aside from basal cell carcinoma or the skin or carcinoma-in-situ of the uterine cervix

The patients were randomized into one of the three groups according to the preset random number. Group A patients were given exemestane 25 mg daily and celecoxib 400 mg twice daily. Group B patients were given exemestane 25 mg alone. Group C patients were given letrozole alone. The treatment will be given as monthly cycles. Each patient will be treated for 3 months and surgery will be performed within 7 days after the last cycle. Therefore, the total duration of treatment was 3 months or up until operation was performed. If operation was refused, the last end-point assessment for inclusion into study should be 90th day after commencement of treatment.

The assessment of tumor diameter was performed before starting treatment and also monthly until completion of neoadjuvant therapy. The clinical assessment will be performed by measurement with calipers. The response was defined according to the standard UICC criteria. Partial response was taken as a 50% or greater reduction in the products of the two maximum perpendicular diameters. Complete response was taken as complete resolution of the tumor.

2.1. Statistical analysis

Parameters were compared using the SPSS for Window release 9.0 (SPSS Inc., USA). One-way ANOVA tests were used to compare means in each group. Fisher's exact test or chi-square test were used to compare the number of events between groups. All values were expressed as mean and standard error of mean (S.E.) unless otherwise stated. $P < 0.05$ was considered as statistically significant.

3. Results

Twenty patients were recruited from May to September 2002. All of them were postmenopausal women. The mean age was 64.4 years (S.E. = 2.88). They were randomized according to the preset number. Nine were randomized to group A, four to group B and seven to group C. As the trial is on going, the results presented here are only from a preliminary analysis.

Fourteen patients completed 2 months and 12 completed 3 months of treatment. Of the 12 patients, five were assigned to be in group A, four in group B and three in group C. Seven patients underwent modified radical mastectomy. The analysis is based on the clinical data collected so far.

The initial largest tumor diameters were 4.61 cm (S.E. = 0.68), 4.13 cm (S.E. = 0.67) and 3.76 cm (S.E. = 0.47) for the respective groups of A, B and C. The original areas for the corresponding groups were 22.21 cm^2 (S.E. = 6.52), 14.2 cm^2 (S.E. = 2.32) and 12.79 cm^2 (S.E. = 2.55). The compliance was good and there was no defaulter. The changes in tumor diameter and area were shown in Figs. 1 and 2. All groups showed clinical response and there was a decrease in tumor area in each group. But the differences were not significant between the three groups. When

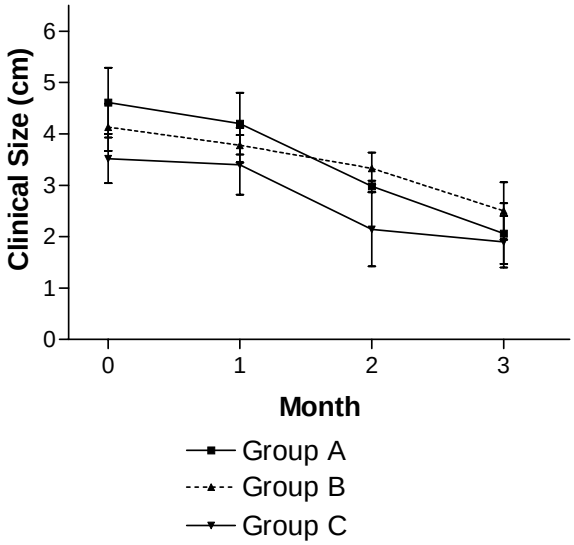

Fig. 1. Reduction in clinical tumor size after three different types of neoadjuvant treatment.

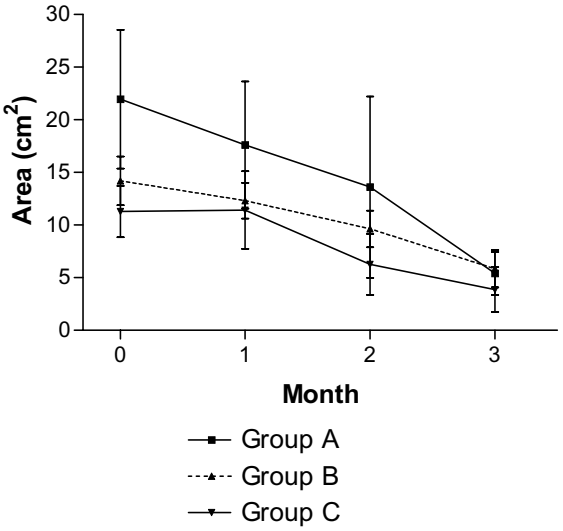

Fig. 2. Reduction in clinical tumor area after three different types of neoadjuvant treatment.

analysis was performed for the 12 patients who had completed 3 months of treatment, there was one complete response and two partial responses in group A, two partial responses in group B and three partial responses in group C. All the other patients had response but not up to 50%. The changes in tumor area for these 12 patients were shown in Fig. 3.

The changes in CEA and CA15.3 were shown in Tables 2 and 3. There was a slight reduction in markers levels. The differences between the three groups were not statistically significant.

Table 2
Changes of blood CEA levels during the period of neoadjuvant treatment

	Pre-treatment	1st month	2nd month	3rd month
Group A	3.33 (0.96)	3.09 (0.73)	3.20 (0.93)	2.0 (0.36)
Group B	2.34 (0.33)	2.40 (0.47)	3.13 (1.26)	2.00 (0.20)
Group C	2.14 (0.38)	1.77 (0.53)	1.57 (033)	0.70 (0.01)

The values in parenthesis represent standard error of mean.

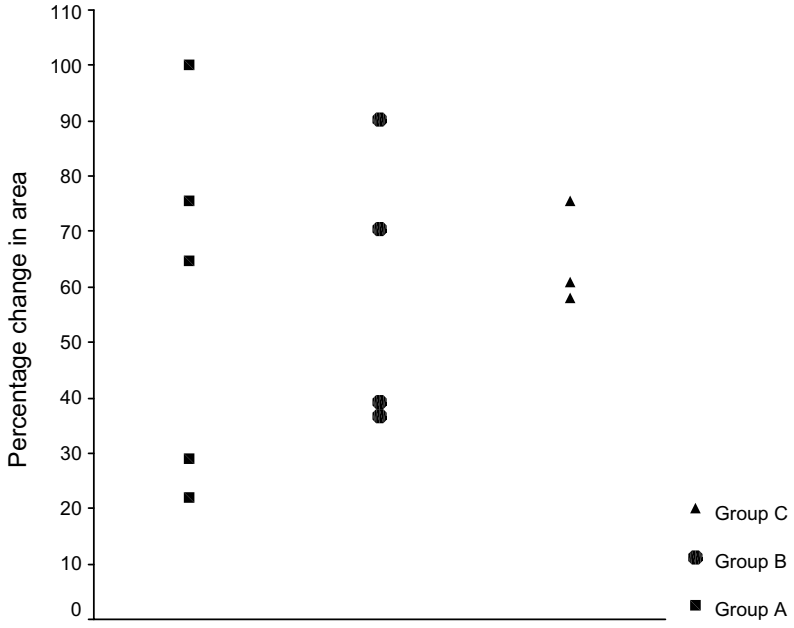

Fig. 3. Percentage reduction from baseline of tumor area for the 12 patients who completed three cycles of neoadjuvant treatment.

Table 3
Changes of blood CA15.3 levels during the period of neoadjuvant treatment

	Pre-treatment	1st month	2nd month	3rd month
Group A	27.96 (8.59)	28.34 (7.54)	18.52 (4.16)	19.17 (11.68)
Group B	39.43 (12.02)	36.41 (12.48)	37.93 (17.06)	23.50 (11.50)
Group C	46.10 (17.33)	18.80 (6.20)	28.00 (0.01)	9.40 (0.01)

The values in parenthesis represent standard error of mean.

4. Discussion

Cyclooxygenase inhibition has been implicated in the blockage of angiogenesis [7,8]. Results from epidemiological studies suggest that use of non-steroidal anti-inflammatory drugs, such as aspirin and indomethacin that inhibit COX-2 activity, reduces the incidence of breast cancer as well as colon cancer in the human [9–13]. Celecoxib is a selective COX-2 inhibitor. It has chemopreventive and chemotherapeutic properties in rodent models of breast cancer [5]. In patients with familial adenomatous polyposis, 6 months of twice-daily treatment with 400 mg of celecoxib leads to significant reduction in the number of colorectal polyps [14].

It is known that the aromatase gene expression is regulated by prostaglandin E_2, which is a product of COX-2 [15]. In fact, there is a linear relationship between aromatase activity and COX-1 and COX-2 expression within the human breast tissue [16]. This significant relationship between the aromatase and cyclooxygenase enzyme systems suggests that autocrine and paracrine mechanisms may be involved in hormone-dependent breast cancer development via growth stimulation from local estrogen biosynthesis. Indeed, recent research on the signaling pathway in the regulation of aromatase and COX-2 expression showed that both the breast epithelial cells and the stromal cell compartment play important roles in the progression of tumor growth [8]. The interconnecting pathway may involve epidermal growth factor (EGF), transforming growth factor-β (TGF-β) and tetradecanoyl phorbol acetate (TPA).

The therapeutic potential of combining celecoxib and exemestane was tested in the DMBA rat model [17]. An objective response rate of 48% was achieved when the rats were treated with both exemestane and celecoxib. This contrasted with OR rates of only 5% when treated with exemestane alone and 0% when treated with celecoxib alone. The development of new tumors follows a similar pattern. The study demonstrated that the addition of celecoxib could enhance the inactivation of aromatase activity.

The CAAN trial is conducted in postmenopausal hormonal-sensitive breast cancer patients to investigate the efficacy of neoadjuvant therapy combining aromatase inhibitors with COX-2 inhibitor. Neoadjuvant treatment of breast cancer offers several advantages. Firstly, the successful therapy would down-stage large tumors to sizes suitable for conservative surgery. Secondly, the sensitivity of the tumor to the therapy administered could be assessed and agents that are effective could be used as adjuvant therapy after the operation. Thirdly, as the breast cancers could be easily accessible, the biological as well as the genetic changes of the tumor could be followed and studied. Recent studies using aromatase inhibitors as neoadjuvant therapy in postmenopausal women have demonstrated that these agents are effective [18–20]. Eleven of the 12 patients given 1 mg and seven of 11 patients given 10 mg of anastrozole had shrinkage of tumors by over 50% [18]. The median reduction from baseline for the whole group was 75.5%. Another non-randomized study showed that letrozole has an apparent superior pathologic response than anastrozole, although the clinical response is similar [19]. Both have a better clinical and pathologic response than tamoxifen. Exemestane treatment was associated with a marked reduction of aromatization peripherally and in non-malignant breast tissue [20]. Eight of the 10 patients that would have required mastectomy were able to undergo breast-conserving surgery after exemestane treatment. There was a median reduction of tumor volume by about 85%.

Based on these results, the CAAN trial is designed to study the neoadjuvant use of exemestane with and without celecoxib. Exemestane is chosen because it is a type I agent and it has marked reduction of aromatization in malignant and non-malignant tissues [20]. In this study, exemestane is given at 25 mg daily with and without celecoxib. Celecoxib is given at 400 mg twice a day. This is the dosage used in the chemopreventive study on familial adenomatous polyposis [14]. A third arm using letrozole 2.5 mg daily is also added as control. The objectives of the study are to confirm the superior laboratory results from treatment combining exemestane with celecoxib, to determine whether the addition of celecoxib would cause different changes in angiogenesis and apoptosis markers, and to evaluate the safety and side effect profiles of the three treatment arms. This preliminary report shows that all of the three anti-aromatase therapies are effective. However, the results presented here are only in the initial phase of the study. It is hoped that at the conclusion of the trial, we would be able to determine the contribution of cyclooxygenase-2 inhibition in the management of hormonal-dependent breast cancers.

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