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Celecoxib and exemestane versus placebo and exemestane in postmenopausal metastatic breast cancer patients: a double-blind phase III GINECO study

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Abstract The aim of this study was to evaluate antitumor effects of cyclooxygenase-2 inhibitors in breast carcinoma and their ability to act synergistically with aromatase inhibitors (AIs). Postmenopausal metastatic breast cancer patients without previous adjuvant AI treatment received exemestane 25 mg/days plus either celecoxib 400 mg twice daily or placebo. The primary endpoint was progression-free survival (PFS). This trial was prematurely terminated ($N = 157$ of 342 planned) after cardiovascular toxicity was reported in other celecoxib trials. Although no PFS difference was observed between the two arms

(9.8 months for both, $P = 0.72$), a trend favoring celecoxib was observed in 60 tamoxifen-resistant patients (9.6 vs. 5.1 months; $P = 0.14$) and in 126 patients treated ≥ 3 months before study termination (12.2 vs. 9.8 months; $P = 0.09$). No severe adverse events were reported. Cyclooxygenase-2 inhibitors seemingly contribute to reverse endocrine resistance in breast cancer patients, although further study is necessary to allow development of a new therapeutic strategy.

Keywords Breast cancer · Celecoxib · Exemestane · Aromatase · Cyclooxygenase-2 · Clinical trial

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Introduction

Despite intensive efforts in cancer control, breast cancer remains the second leading cause of cancer death in western countries [1, 2]. In the metastatic setting, it is widely accepted that the main objective is to maintain good quality of life for patients as long as possible [3]. For the majority of patients with hormone receptor-positive, slowly progressing tumors, endocrine therapy appears to be the treatment of choice [4–6]. For postmenopausal women, hormone therapy with an aromatase inhibitor (AI) is a standard first-line treatment for women who were not treated with an AI in the adjuvant setting, although median time to progression for these patients is ~ 8 –11 months, with no demonstrated survival advantage over tamoxifen [7–10]. Consequently, to increase the therapeutic benefit of hormone therapy, new approaches are still needed.

Prostaglandins can enhance carcinogenesis by inducing cell proliferation, suppressing apoptosis, stimulating angiogenesis and invasiveness, and inhibiting immune responses [11–15]. Prostaglandin synthesis from arachidonic acid is

mediated by cyclooxygenase (COX)-1 and COX-2 isoenzymes. Most tissues that normally produce prostaglandins have constitutive expression of COX-1 [16], whereas COX-2 expression is induced by mitogens, hormones, serum, and cytokines [16], leading to localized acute inflammatory responses. COX-2 expression is also upregulated in some human premalignant and malignant pathologies [17], including breast cancer [18]. Moreover, transgenic mice that overexpress human COX-2 in mammary glands develop focal mammary gland hyperplasia, dysplasia, and metastatic tumors [19]. In contrast, tumor-prone MMTV/*neu* mice that were made to be COX-2-deficient develop fewer, smaller tumors with substantially reduced vascular infiltration than mice expressing COX-2 [20]. Thus, COX-2 has become an attractive target for inhibiting tumor growth.

Nonsteroidal anti-inflammatory drugs (NSAIDs) that are not selective for COX-2, such as ibuprofen and aspirin, have demonstrated therapeutic potential against breast cancer in an epidemiologic case-control study [21]. In addition, celecoxib analogs, some of which are selective COX-2 inhibitors, were shown to be potent inhibitors of phospho-Akt-signaling pathways and to induce apoptosis in breast cancer cells in vitro [22, 23]. Studies with animal models of breast cancer have demonstrated that treatment with selective COX-2 inhibitors reduced the formation, growth, microvasculature, and metastases of tumors [13, 23–26]. Furthermore, selective COX-2 inhibitors have been shown to reduce the number of intestinal tumors in patients with familial adenomatous polyposis [27, 28].

Despite the inability to correlate increased COX-2 expression with upregulated hormone receptors, COX-2 overexpression leads to a proximal activation of the aromatase gene [29]. AIs and COX-2 inhibitors were shown to have a synergistic antitumor activity in a rat model of mammary carcinoma [30], and the association has also been tested in clinical trials, in both adjuvant and metastatic settings, with promising preliminary results in limited numbers of patients [31–33].

The aim of this study was to compare the efficacy of the combination of the AI exemestane and the COX-2 inhibitor celecoxib with exemestane + placebo in a first-line metastatic setting in postmenopausal women with hormone receptor-positive breast cancer.

Methods

Patients

Postmenopausal women with estrogen receptor- and/or progesterone receptor-positive metastatic breast cancer with measurable lesions >1 cm in diameter were eligible for enrollment. Inclusion criteria included an Eastern

Cooperative Oncology Group performance status ≤ 2 and adequate hematologic, renal, and hepatic function (serum bilirubin $\leq 2 \times$ upper limit of normal [ULN], alanine aminotransferase and aspartate aminotransferase $\leq 2 \times$ ULN or $\leq 4 \times$ ULN if hepatic metastases, alkaline phosphatase $\leq 2 \times$ ULN or $\leq 5 \times$ ULN if hepatic metastases). Patients with isolated bone metastases with typical radiologic lesions and an associated increase in cancer antigen (CA) 15-3 were eligible, but not patients with isolated CA 15-3 increases. Exclusion criteria included prior adjuvant treatment with an AI; endocrine therapy for metastatic cancer; and ongoing treatment with an NSAID, fluconazole, lithium, or warfarin. Patients with an allergy to NSAIDs, an uncontrolled cardiac comorbidity (e.g., angina or congestive heart failure), or a history of myocardial infarction within 3 months were also excluded. However, previous chemotherapy for metastases was permitted.

Study design

This was a multicenter, double-blind, randomized phase III study conducted at 62 sites in France. The study, sponsored by Pfizer Inc, was conducted independently by the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers de l'Ovaire et du Sein (GINECO) according to the principles of the Declaration of Helsinki, and the protocol was approved by the Independent Ethics Committee of Paris Hôtel Dieu Hospital. All patients provided written informed consent. At study entry, patients underwent baseline evaluations that included a complete medical history and physical examination; assessment of performance status; and biologic evaluation of CA 15-3 levels and hematologic, renal, and hepatic functions. Standard radiologic screening at baseline included computed tomography scans of the chest, abdomen, and pelvis and a bone scan. All patients received exemestane 25 mg daily. In addition, patients were randomly assigned to receive celecoxib 800 mg (400 mg twice daily) or placebo. No dose reductions were planned. Randomization was performed by stratified block permutation. Stratification was done according to the center, previous chemotherapy for metastatic disease, and presence of visceral lesions. Physical examinations were performed, symptoms and/or adverse events (using the National Cancer Institute Common Toxicity Criteria Version 2.0) were assessed, hematology and blood chemistry profiles including CA 15-3 were obtained, and tumor response was monitored every 2 months. A complete set of imaging tests was planned at 2 months, every 6 months thereafter and whenever clinically indicated.

Statistical analysis

The primary study endpoint was progression-free survival (PFS). Secondary objectives included assessments of tumor

response and toxicities. A minimum of 171 patients per treatment group with a minimum follow-up of 1 year were required to provide 90% power to detect a difference in PFS at 1 year of 15% (from 35 to 50%) with a 2-sided significance of 5%. PFS was measured from the date of study enrollment to clinical or radiologic progression or death, or censored at date of last contact. Analyses for efficacy were performed on the intent-to-treat population on a per-protocol basis. Efficacy was assessed by the treating physician and was systematically reassessed by a review panel following Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. No intermediate analysis was planned; however, because of the premature termination of the study, a supplementary analysis of the patients who were enrolled ≥ 3 months before study termination was also performed. The subgroup of patients with tamoxifen-resistant disease (defined as relapse during or within 12 months of completion of tamoxifen therapy) was also assessed.

Progression-free survival was analyzed using Kaplan–Meier analysis, and the predictive role of pretreatment covariates was estimated in univariate analysis, using log-rank tests. Response rates were compared using the Fisher exact test. For toxicity comparisons, the Mann–Whitney U test could be supplemented with the Fisher exact test for values with normal distribution. Statistical analysis was independently performed.

Results

Patients

Because of notification in December 2004 of cardiovascular toxicities in other trials with celecoxib [34], the sponsor of this trial decided to terminate the study prematurely. Between September 2003 and December 2004, 157 patients were enrolled in 27 centers. Patient characteristics at baseline were well balanced between treatment groups (celecoxib + exemestane, $n = 74$; placebo + exemestane, $n = 83$; Table 1). Although slightly more patients in the placebo group had multiple metastases and visceral disease at study entry, these differences were not significant ($P = 0.77, 0.20$, respectively). The median duration of treatment was 5.8 months (6 months celecoxib vs. 5.6 months placebo, $P = 0.6$). At the time of the sponsor's decision to terminate the study, 85 patients were still receiving treatment (celecoxib, $n = 43$; placebo, $n = 42$). The administration of celecoxib and placebo was stopped, but treatments were not unblinded; exemestane monotherapy was continued until disease progression was observed. Before study termination, 31 and 41 patients had discontinued treatment in the celecoxib and placebo arms,

Table 1 Patient demographics

Characteristic	Celecoxib + exemestane	Placebo + exemestane	<i>P</i> value
Patients, <i>n</i>	74	83	
Age (years)			
Median	61	63	
Range	38–84	37–82	
Hormone receptor status (%)			
ER+ and/or PgR+	93	94	0.44
HER2+	4	5	0.83
Adjuvant chemotherapy (%)	45	53	0.34
Adjuvant tamoxifen (%)	57	61	0.63
Performance status (%)			0.34*
0	50	43	
1	41	47	
2	7	10	
Unknown	3	0	
Metastatic site (%)			
Visceral	37	47	0.20
Liver	20	19	1.00
Lung/pleura	18	29	0.13
Lymph node	26	25	1.00
Soft tissue	14	10	0.67
Bone (isolated)	35	41	0.49
Number of metastatic sites (%)			0.78*
1	67	56	
2	22	30	
>2	14	14	

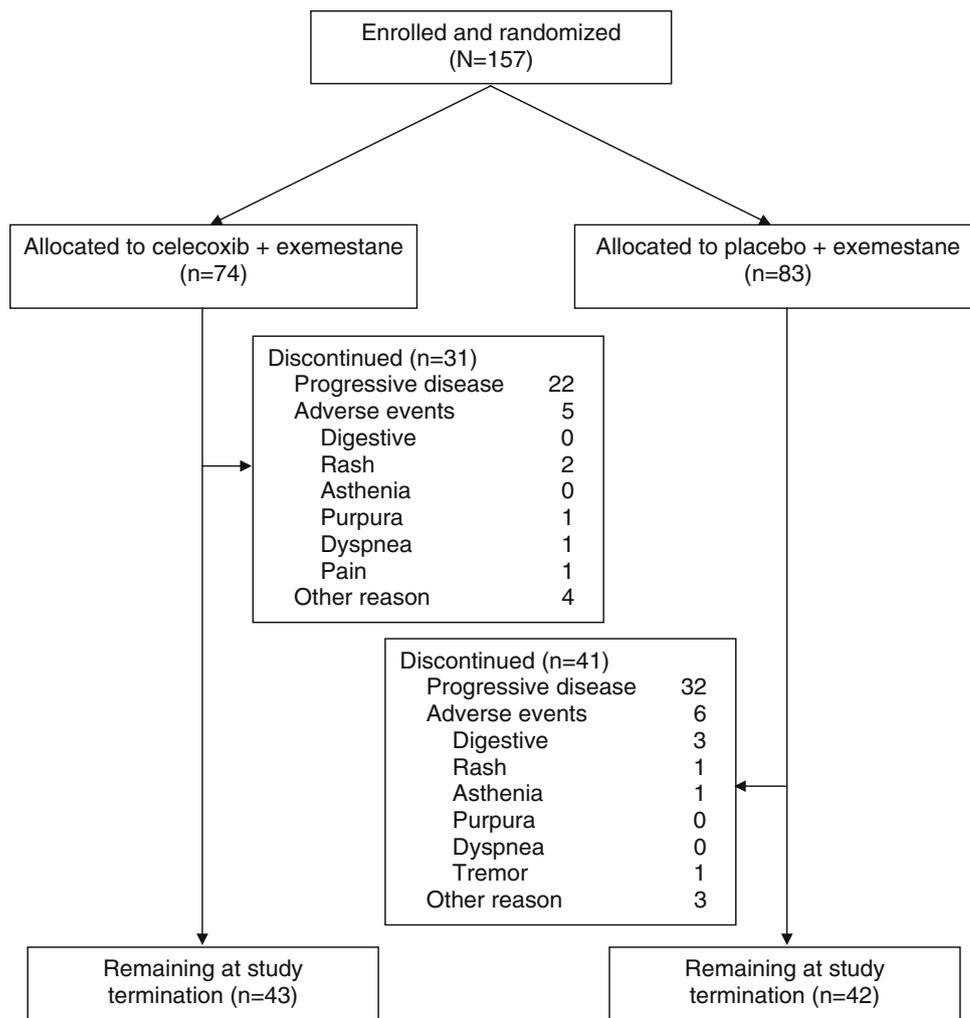
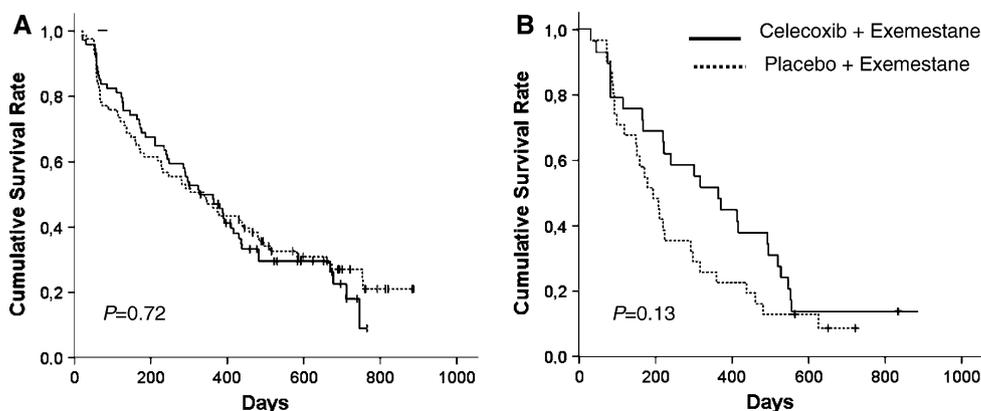
ER estrogen receptor; HER2 human epidermal growth factor receptor 2; PgR progesterone receptor

* *P* value for the overall comparison

respectively. Eleven patients discontinued treatment because of toxicity (celecoxib, $n = 5$; placebo, $n = 6$). Patient disposition and reasons for discontinuation are shown in Fig. 1.

Efficacy

Of 157 patients enrolled in the study, 146 were evaluable for disease response and 140 were reassessed by a review panel. The median follow-up was 24 months, and the median PFS in the intent-to-treat analysis was the same in both treatment groups (9.8 months, $P = 0.72$; Fig. 2a). Although the difference was not significant, PFS appeared to be numerically longer for patients receiving celecoxib compared with those receiving placebo in the subgroup of tamoxifen-resistant patients [9.6 months ($n = 29$) vs. 5.1 months ($n = 31$)], respectively; $P = 0.14$; Fig. 2b); a similar trend favoring patients in the celecoxib arm was also

Fig. 1 Patient disposition**Fig. 2** Progression-free survival. **a** Intent-to-treat population ($n = 157$). **b** Patients resistant to adjuvant tamoxifen ($n = 60$). Resistance is defined as relapse while being treated with tamoxifen or within 1 year after completion of treatment

observed in the subgroup of patients treated ≥ 3 months before the termination of the study [12.2 months ($n = 56$) vs. 9.8 months ($n = 70$), respectively; $P = 0.09$]. The PFS difference between the celecoxib and placebo arms was significant in tamoxifen-resistant patients treated for ≥ 3 months [8.4 months ($n = 21$) vs. 4.7 months ($n = 21$), respectively; $P = 0.019$]; this subgroup analysis was not

preplanned. Based on RECIST guidelines, the difference in response rate assessed by a review panel was not statistically significant (24% vs. 17%, $P = 0.18$; (Table 2). Disease progression was observed in 22 (30%) and 32 (39%) patients in the celecoxib and placebo groups, respectively ($P = 0.236$), with median durations of response of 5.8 months and 4.1 months ($P = 0.250$).

Table 2 Overall response rate

	Celecoxib + exemestane, <i>n</i> (%)	Placebo + exemestane, <i>n</i> (%)	<i>P</i> value
Overall response rate	15 (24)	13 (17)	0.18
Complete	1 (2)	0 (0)	
Partial	14 (23)	13 (17)	
Stable disease	34 (55)	44 (56)	

Safety

Treatment with celecoxib and exemestane was generally well tolerated. The majority of toxicities were grades 1 and 2 (Table 3). Toxicities reported with the highest overall frequencies for patients receiving celecoxib and placebo, respectively, were pain (70 vs. 77%, $P = 0.33$), arthralgia (32 vs. 43%, $P = 0.16$), asthenia (43 vs. 48%, $P = 0.54$), and insomnia (39 vs. 49%, $P = 0.20$). Patients treated with celecoxib experienced less grade 2 or 3 pain, arthralgia, asthenia, and insomnia and more hypersensitivity reactions (7 vs. 0%) and edema (8 vs. 2%); all between-group differences were nonsignificant. Gastrointestinal toxicity did not differ in the two arms. One patient with a history of cardiopathy who was treated with celecoxib + exemestane experienced paroxysmal arrhythmia without any cardiac complication.

Discussion

Results from several clinical trials have demonstrated the antitumor activity of celecoxib in patients with breast cancer in preventive or therapeutic settings [31, 32, 35, 36]. COX-2 inhibitors are thought to inhibit tumors by indirectly affecting estrogen production. Increased prostaglandin E₂ (PGE₂) produced by the activity of the COX-2 enzyme is associated with upregulation of the aromatase enzyme, which in turn leads to increased local estrogen synthesis [29, 37]. These higher estrogen levels stimulate growth and proliferation of a number of breast cancers. By reducing production of PGE₂, COX-2 inhibitors reduce the available estrogen required to maintain the tumors. Therefore, combination therapy with COX-2 inhibitors and AIs was evaluated in several clinical trials [31, 32, 38]. Clinical benefit was achieved in 74% of patients in a preliminary study of 53 postmenopausal women with histologically confirmed hormone receptor-positive advanced breast cancer treated with exemestane and celecoxib [31].

This study was underpowered because of premature termination and did not demonstrate a PFS difference between treatment groups. Despite the relatively small

Table 3 Toxicity

Toxicity	CTC AE grade	Celecoxib + Exemestane, <i>n</i> (%)	Placebo + Exemestane, <i>n</i> (%)
Alopecia	1	3 (4)	2 (2)
Anorexia	1	1 (1)	0 (0)
Arthralgia	1	10 (13)	13 (16)
	2	9 (12)	15 (18)
	3	5 (7)	8 (10)
Asthenia	1	17 (23)	16 (19)
	2	14 (19)	23 (28)
	3	1 (1)	1 (1)
Cardiac arrhythmia	3	1 (1) ^a	0 (0)
Dysesthesia	1	1 (1)	1 (1)
	2	0 (0)	1 (1)
Dyspnea	1	0 (0)	1 (1)
Edema	1	5 (7)	5 (6)
	2	6 (8)	2 (2)
	3	0 (0)	0 (0)
Gastrointestinal difficulties	1	0 (0)	1 (1)
	2	3 (4)	2 (2)
Hepatic cytolysis	1	0 (0)	2 (2)
	2	1 (1)	0 (0)
Hypersensitivity reaction	1	1 (1)	3 (3)
	2	3 (4)	0 (0)
	3	2 (3)	0 (0)
Insomnia	1–2	24 (32)	39 (47)
	3	5 (7)	2 (2)
Mucositis	1	3 (4)	1 (1)
	2	1 (1)	0 (0)
Pain	1	13 (18)	12 (14)
	2	28 (38)	30 (36)
	3	11 (15)	22 (27)
Rash	1	5 (7)	6 (7)
	2	2 (3)	4 (5)
	3	4 (5)	2 (2)
Visual difficulties	1	0 (0)	1 (1)
Weight decrease	1	0 (0)	1 (1)
Weight increase	3	0 (0)	1 (1)

CTC AE common toxicity criteria for adverse events

^a Observed in a patient with a history of arrhythmia

numbers of patients remaining after premature termination of the study (median time on study treatment was 6 months), we elected to examine the effects of the combination therapy on PFS in 2 subpopulations. Previous preliminary evaluations demonstrated improved antitumor response in patients with breast cancer treated with exemestane and celecoxib for >3 months [32]. In the current study, the cohort of patients who were treated for ≥3 months before trial termination had a PFS that was

numerically better for patients treated with celecoxib compared with placebo (12.2 vs. 9.8 months, respectively; $P = 0.09$). However, this difference was not significant, nor was it observed in the entire study population. Among tamoxifen-resistant patients (i.e., those who developed metastatic disease during therapy with tamoxifen or within 12 months after completion of tamoxifen treatment), PFS was significantly greater in patients who received the combination therapy for ≥ 3 months (8.4 vs. 4.7 months with placebo, $P = 0.019$). Several potential explanations exist for these isolated improvements. Could this subgroup potentially consist of patients who lost hormone sensitivity during tamoxifen treatment and thus no longer responded to endocrine therapy alone (including AIs)? Although this may explain the lower median PFS for patients treated with AIs alone in the tamoxifen-resistant group compared with the broader trial (4.7 vs. 9.8 months, respectively), it would still reinforce an added antitumor activity of celecoxib in the advanced breast cancer setting. Or, is COX-2 overexpression highly variable but more specific in the relatively aggressive tamoxifen-resistant tumors? This also raises the potential question of whether to initiate “targeted” use of anti-COX-2 treatments focused on COX-2 overexpressing tumors. Although these subgroup analyses were not intended in the original study design, the preliminary results should be considered in designing future studies.

In this study, concomitant treatment with celecoxib and exemestane was well tolerated. Patients treated with the combination had less pain, arthralgia, and insomnia, all of which have been observed in previous studies with AIs [31, 39]. However, in December 2004, cardiovascular toxicity concerns led the National Cancer Institute to terminate a study investigating the use of celecoxib to prevent colon polyps [34, 40]. Subsequently, the US Food and Drug Administration (FDA) issued a Public Health Advisory regarding continued use of COX-2 inhibitors [41], and studies for several indications, including cancer prevention, arthritis, and osteoarthritis, were prematurely halted. Later, an FDA advisory committee recommended continued use of COX-2 inhibitors with safety warnings highlighting the increased risk for cardiovascular toxicity [42]. Because the cardiotoxicity associated with COX-2 inhibitors appears to be progressive and cumulative, it is not surprising that it was not observed during this study, with the exception of arrhythmia in a patient with a history of cardiopathy. The median duration of treatment (6 months) of the small population here was substantially shorter than the 2.8–3.1 years of follow-up in the Adenoma Prevention With Celecoxib study [34].

The hypothesis of the current study was that the use of AIs concomitantly with inhibitors of promoter II of the cytochrome P450 (CYP) 19 gene could be clinically relevant because the two drugs may act synergistically.

However, considering the known cardiotoxicity risk associated with COX-2 inhibitors, another strategy is to focus on different regulators of aromatase expression, such as the nuclear receptor liver receptor homolog-1 (LRH-1) [43, 44]. A major advantage to this concept is that CYP19 uses ≥ 9 different promoters that are at least partially tissue specific [45]. Thus, the strategy of targeting CYP19 promoters in breast cancer tissue has the potential to be highly tolerated.

Although the results from this study did not show a significant benefit for the combination treatment in patients with metastatic breast cancer, this regimen should be the subject of further evaluation with adequate cardiac monitoring. To further support this proposal, a meta-analysis is in preparation that will pool results from three trials using COX-2 inhibitors in combination with exemestane in patients with metastatic breast cancer to allow evaluation of efficacy of this treatment regimen in a sufficiently large patient population.

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