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A feasibility study of the efficacy and tolerability of the combination of Exemestane with the COX-2 inhibitor Celecoxib in post-menopausal patients with advanced breast cancer

P.A. Canney[a,*], *M.A. Machin*[b], *J. Curto*[b]

[a]*Beatson Oncology Centre, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, UK*
[b]*CRCUK clinical Trials Unit, Western Infirmary, Dumbarton Road, Glasgow, UK*

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ABSTRACT

Background: This was a feasibility study of the combination of Exemestane and the cyclo-oxygenase-2 (COX-2) inhibitor Celecoxib in advanced breast cancer.

Patients and methods: Post-menopausal women with histologically proven, hormone receptor positive, advanced breast cancer who had progressive disease, normal blood counts, liver and renal function were eligible. Exemestane was given at a dose of 25 mg daily and Celecoxib at a dose of 400 mg bd. Responses were assessed according to RECIST criteria and toxicity was accessed according to CTC. The primary end-point was the percentage of patients who had neither discontinued therapy nor progressed at 6 months ('treatment successes').

Results: Fifty-three eligible patients were enrolled. Of 30 patients with target lesions, 4 (13%) had a complete response (CR), 12 (40%) a partial response (PR) and 5 (17%) stable disease (SD). The best response in 18 of the 23 patients with no target lesions at baseline was stable disease. The clinical benefit (CR, PR + SD) for the whole group was therefore 39/53 (74%). The 'treatment success' rate was 60%. There were two non-malignant deaths which may have been associated with treatment.

Conclusion: The combination of Exemestane and Celecoxib shows promising activity and tolerability and these results support the use of this combination in phase III clinical trials of short duration treatments.

1. Introduction

Advanced metastatic breast cancer (MBC) is an incurable condition with a relatively long clinical course. The development of drugs with increased activity and/or reduced toxicity is desirable in order to shift the balance further in favour of clinical benefit and improved quality of life.

Cyclo-oxygenase-2 (COX-2) has been shown to be present in a varying proportion of patients with breast cancer, and is associated with poorer prognostic features.[1] COX-2 catalyses key steps in the metabolism of arachnadonic acid to prostaglandins and eicosanoids. COX-2 is inducible and not found expressed in normal tissue but only in inflammatory diseases and malignant transformation. When in response to stimuli,

* *Corresponding author:* Tel.: +44 141 211 1743; fax: +44 141 211 1866.
E-mail address: peter.canney@northglasgow.scot.nhs.uk (P.A. Canney).
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cells express COX-2, they develop a resistance to apoptosis and develop changes in their adhesion properties.[2] COX-2 expression is secondary to mitogenic events such as Ras mutations and loss of p53.[3] There have been responses to COX-2 inhibitors (Celecoxib) alone reported in some animal cancers,[3,4] and they are currently being investigated as inhibitors of carcinogenesis in colorectal cancer.[5] COX-2 also affects angiogenesis and COX-2 inhibitors can reduce vascular density in experimental tumours and decrease VEGF levels.[6,7] There has only been one randomised clinical trial of NSAIDs in patients with various malignancies, which showed that patients taking indomethacin had significantly less pain and increased mean survival than controls.[8]

Specifically, in the cases of hormone sensitive tumours PGE2, the final active compound of arachnadonic acid metabolism can stimulate CYP19 the aromatase gene. Therefore, COX-2 derived PGE2 may also modulate cellular proliferation through stimulation of oestrogen biosynthesis within breast tumours,[9–12] and is a potential mechanism for breast cancer induction and resistance to systemic aromatase inhibition. COX-2 expression also correlates with progesterone receptor expression.[13]

COX-2 has been shown to be present in a varying but significant proportion of patients with breast cancer. Most breast cancers that are HER2 positive express COX-2 immunocytochemically, and HER2/neu stimulates COX-2 transcription via the Ras-MAPK pathway.[14]

Exemestane is a steroidal aromatase inhibitor which has been shown to be more active than megace[15] and tamoxifen[16] in the treatment of metastatic breast cancer. The biological effects of COX-2 inhibition suggest that a combination of COX-2 inhibitor with an aromatase inhibitor may potentially improve the efficacy of aromatase therapy in clinical practice. However, this combination required testing to ensure that it is tolerable and not detrimental in terms of efficacy of Exemestane alone. This report presents the final results of a phase II trial of the combination of Exemestane and the COX-2 inhibitor Celecoxib.

2. Patients and methods

2.1. Patient population

Inclusion and exclusion criteria are shown in Table 1. All patients were post-menopausal with known ER positive locally advanced or metastatic breast cancer at first relapse. The participants were recruited from those attending specialist breast oncology clinics at the Beatson Oncology Centre, Western Infirmary, Glasgow, Scotland.

This study was conducted in agreement with the Declaration of Helsinki (Edinburgh, Tokyo, Venice, Hong Kong and Somerset West amendments). The protocol was written, and the study conducted according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice. The Local Ethics Committees approved the protocol, and all patients gave written informed consent.

2.2. Study design

The principal objective of the trial was to assess the percentage of patients who neither discontinued therapy nor progressed at 6 months ('treatment successes'). Secondary objectives were response rates, duration of response, time to next progression, toxicity graded according to the 'common toxicity criteria' version 2.0 (CTC)[17] and quality of life (QOL) at baseline and 3 monthly (measured by EORTC QLQ C-30 v3.0 and QLQ-BR23).

Exemestane (Aromasin) was given in the standard dose of 25 mg daily, and Celecoxib (Celebrex) was given at a dose of 400 mg bid. There were no dose modifications allowed for Exemestane. The dose of Celebrex could be reduced to 200 mg bid if moderate or severe toxicity occurred. Treatment was administered until documented disease progression, unacceptable toxicity, or patient refusal.

Concomitant cytotoxic or hormonal therapies were not allowed. Tamoxifen, if previously given, must have been discontinued prior to initiation of the study drug. Bisphosphonates given for bony disease were not allowed, but radiotherapy for symptomatic lesions was allowed, provided that the irradiated area did not contain the sole target lesion, and provided that this was within 8 weeks of starting therapy. The use of palliative radiotherapy after 8 weeks on study equated to disease progression.

Response evaluation conformed to the RECIST system.[18] The initial assessment of the disease (including measurement of all target lesions) was performed within 3 weeks prior to the first treatment administration. Follow-up assessments were performed at 8 weeks, and every 3 months thereafter until disease progression, or until the start of another treatment. In case of detection of a complete or partial response, a confirmation assessment was performed not less than 4 weeks after the first documentation of the response.

Treatment side-effects were assessed separately for each period of therapy, at 4 weeks, 8 weeks and 3 monthly thereafter using the CTC. All eligible patients who started treatment were included in the overall toxicity analyses. The worst grade of each toxicity thought to be at least possibly related to treatment was tabulated. The patients who discontinued treatment because of toxicity were included in the response and toxicity analyses.

2.3. Statistical methodology

The basic hypothesis was that if the percentage of treatment successes (patients who had not progressed and were still receiving treatment at 6 months) was $\geqslant$50%, the treatment is clearly feasible and should be considered for future testing in a phase III setting; alternatively if the percentage of treatment successes was $\leqslant$30%, then further testing of this combination is not warranted. To distinguish between these two alternatives, a Simon two-stage minimax design was used with 90% power and 5% one-sided level of statistical significance; this required a maximum of 53 patients. For this design 24 patients are recruited in the first stage, and if 7 or fewer successes are observed, the trial is stopped with the conclusion that the successess rate is $\leqslant$30%. If 8 or more successes are observed in the first stage a further 29 patients will be recruited. If 22 or more success are observed over the two stages, then it is concluded that the success rate is $\geqslant$50%.

All patients were followed-up for a minimum of 12 months before the final analysis was undertaken. All eligible patients

Table 1 – Inclusion and exclusion criteria

To be eligible for participation in this trial, patients had to satisfy ALL of the following inclusion criteria
Histologically proven breast cancer
No other malignancy, except non-melanoma skin cancer or CIN
Age >18 years
Post-menopausal
Performance status 0, 1 or 2 (ECOG)
Metastatic or locally advanced disease
Oestrogen receptor and/or progesterone receptor positive
WCC >3.5 and platlets >100,000
AST, ALT <2× upper limit of normal range, bilirubin
<1.5 normal range, alkaline phosphatase <2× normal (unless bone metastases present)
Normal renal function
Suitable for hormone therapy
Written informed consent obtained according to local ethics committee guidelines
Patients meeting any ONE or more of the following criteria were ineligible to participate in this trial
Brain metastases
Severe concurrent illness
Unable to comply with follow-up
Any prior therapy for metastatic disease/locally advanced disease other than tamoxifen
History of hypersensitivity to sulphonamides
Concurrent use of NSAIDs
The presence of any psychological, familial, sociological or geographical condition that may potentially hamper compliance with the study protocol and follow-up schedule

were included in the data analysis (except response, see below). For the primary end-point, the percentage of treatment successes are reported with the associated 95% confidence interval. The response analysis was restricted to patients with at least 1 target lesion. Time to progression was analysed for all patients. Duration of response, survival and progression-free survival were estimated using Kaplan–Meier techniques.

The EORTC QLQ C-30 + QLQ-BR23 module was used to assess quality of life (QOL). The average value of the various scales prior to treatment failure for each patient were compared to baseline value using the Wilcoxon signed rank method.

3. Results

Between March 2002 and August 2003, 54 patients were entered into the trial. One patient withdrew consent before starting any treatment and has been excluded from further analysis.

Patient demographics are shown in Table 2. Thirty-six percentage of patients had visceral disease and there was an average of 1.4 disease sites per patient. Twenty-six patients had previously received Tamoxifen as adjuvant treatment, the mean interval between stopping Tamoxifen and starting study registration was 388 (range 0–2754) days. Sixteen patients had received Tamoxifen for metastatic or locally advanced disease, the mean interval between stopping Tamoxifen and starting study registration for this group 94 (range 0–1114) days. Thirteen patients had received adjuvant chemotherapy.

Nine patients stopped treatment for reasons other than progression, 2 due to toxicity and 3 due to 'medical decision' by their family practitioners, 1 due to renal function impairment and 3 deceased (1 CVA, 1 pulmonary embolism and 1 malignant disease). Eight patients had a dose reduction of Celecoxib: 3 due to possible toxicity, 4 due to prescribing error and 1 due to unknown reason.

3.1. *Response*

The percentage of patients who had neither discontinued treatment nor progressed at 6 months, 'treatment successes', was 60%, 32/53 (SE = 6.7%, 95% confidence interval 47–74%), and at 12 months was 46% (SE 7%) (see Table 3).

Table 2 – Patient demographics

Performance status		
1	17	32%
2	26	49%
3	10	19%
Oestrogen receptor		
Positive	53	100%
Progesterone receptor		
Positive	20	38%
Negative	2	4%
Unknown	31	58%
Disease site		
Bone	33	62%
Liver	9	17%
Lung	14	26%
Soft tissue	17	32%
Adjuvant chemotherapy	13	25%
Previous tamoxifen		
Adjuvant	29	55%
Metastatic/locally advanced	19	36%

Table 3 – Overall response rates

	Best overall response	Number	Percent (%)
Patients with target lesions (N = 30)	CR	4	13
	PR	12	40
	SD	5	17
	CR + PR + SD	21	70
	PD	4	13
	Not re-assessed	5	17
Patients without target lesions (N = 23)	SD	18	78
	PD	4	17
	Not reassessed	1	4
Whole group	Clinical benefit (CR + PR + SD)	39	74

Thirty patients had target lesions and could therefore be assessed for overall response. The response rate (CR + PR) was 16/30 (53%) with a further 5 patients (17%) having stable disease (Table 3). A total of 23 patients had only non-target lesions at baseline and of these 18 (78%) had static disease. By combining the best overall response of patients with target lesions and non-target lesions, the overall Clinical Benefit Rate (CR + PR + SD) was 39/53 (74%). Six patients did not have formal reassessment of disease for response: 4 due to rapidly progressive disease or early death and 2 had therapy stopped for reasons other than progression. All 6 were counted as treatment failures.

3.2. *Duration of response and survivals*

The duration of responses was calculated for the 16 patients with best overall response being CR or PR. The median duration of response was 89 weeks (SE, 11.3 weeks).

Progression free survival (PFS) is shown graphically in Fig. 1. The overall PFS at 6 months was 72% (standard error (SE) = 6.2%) and at 12 months was 53% (SE = 7.1%). This result differs from the 'treatment success' result due to those patients who stopped therapy without having progressed.

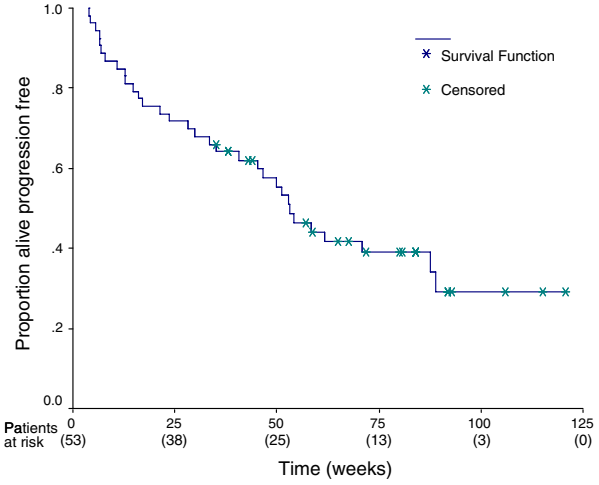

Fig. 1 – Progression free survival.

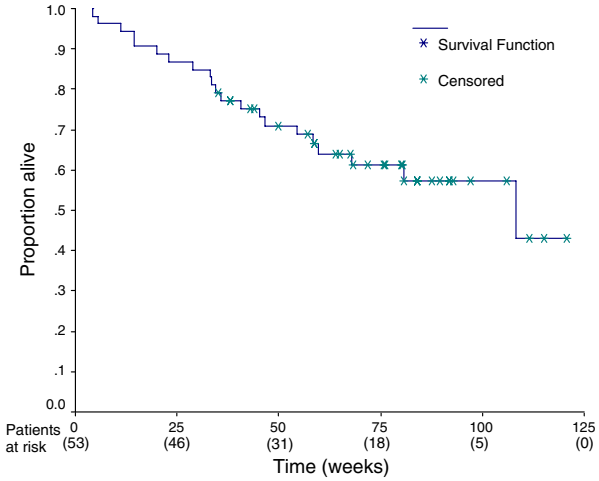

Fig. 2 – Overall survival.

Overall survival is shown in Fig. 2. The median follow-up for living patients is 78 weeks (range 35–121 weeks). Twenty-one patients have died, 17 from malignant disease, 1 from a pulmonary embolus, 1 from a cerebral vascular accident and 1 from a surgical complication. The cause of death for 1 patient is unknown. The percentage of patients alive at 6 months was 87% (SE = 7%) and at 12 months was 71% (SE = 6%).

3.3. *Toxicity*

Toxicities occurring in >10% of patients are listed in Table 4. One patient died of surgical complications 2 weeks after having repair of a perforated gastric ulcer, after being on treatment for 24 weeks, but also had progression of her metastatic breast cancer at the time. Two patients stopped treatment due to excessive toxicity: one at 4 weeks due to oesophagitis and one at 24 weeks due to diarrhoea. There was no significant haematological or biochemical toxicity. One patient had grade 3 arthralgia, but only 2 further patients had arthralgia probably related to treatment, one of these grade 1 and the other grade 2.

Table 4 – Toxicities occurring in >10% of patients

Toxicity	CTC grade	Number	Percent (%)
Dyspepsia/Heartburn	1	2	
	2	3	
	3	1	
	All grades	6	11
Hot flushes/night sweats	1	5	
	2	6	
	3	2	
	All grades	13	25
Nausea	1	3	
	2	2	
	3	2	
	All grades	7	13

3.4. *Quality of life*

The average value of the scales recorded in all the QOL forms prior to treatment failure was compared to baseline using the Wilcoxon signed test. Statistically significant differences were found in only two of the scales assessed. The first was the constipation scale, showing less perception of constipation symptoms during treatment than at baseline (mean change = 10, SE 3.7, $p = 0.013$). The second was in the Future Perspective Scale which measures the patient's concerns about her future health. This showed a higher level of concern during treatment than at baseline (mean change = 8.8, SE 3.5, $p = 0.015$).

4. Discussion

Despite the third generation aromatase inhibitors, including Exemestane, being a significant improvement over previously available therapies, about half of oestrogen receptor positive patients still fail to get any clinical benefit.[14,15] There are likely to be multiple reasons for this, and it would also seem likely that there will be inter-patient variation in the mechanisms of failure with possibly more than one reason for any individual patient. COX-2 inhibitors do not target a single specific growth factor pathway but, as mentioned in the introduction, there are several plausible prima facie reasons for the combination of an aromatase inhibitor with a COX-2 inhibitor to be of interest. At present which of the potential interactions may be significant clinically is a matter for speculation and further biological studies in the neo-adjuvant setting are required to attempt to elucidate which of these mechanisms of interaction between COX-2 and aromatase inhibitors may operate.

This was a phase II feasibility study of the combination of Exemestane with Celecoxib as first line therapy for post-menopausal women with locally advanced or metastatic breast cancer. Formal responses were noted for those patients with measurable disease, but the primary end-point of efficacy was assessed by indirect measurement using the percentage of patients who had neither discontinued therapy nor progressed at 6 months ('treatment successes') and time to next progression. This approach was similar to, but more rigorous, the more familiar 'clinical benefit' parameter (CR + PR + Stable Disease at six months) and allowed a wider, more representative, group of patients to be entered. In particular, those with predominantly bone or bone only metastases were included. Although generally thought to have a better prognosis in the longer term[19], in this study there was no difference in outcome for those patients with bone as the dominant or only site of metastases compared to those with measurable soft-tissue and/or visceral disease (Table 3). Nineteen percentage of patients had a performance status of 3 at entry: a group also usually excluded from clinical trials but commonly seen in routine clinical practice.

For the primary end-point, a Simon two-stage minimax design used required that 22 or more treatment successes were observed over the two stages to conclude that the success rate was $\geqslant$50% with 90% power and 5% level of statistical significance. The success rate demonstrated here was 32 patients, comfortably exceeding the required target, and therefore the addition of Celecoxib to Exemestane is not detrimental in this population of patients. In the subgroup of 30 patients who had target lesions as defined by RECIST criteria, the secondary end-point of response rates compared favourably with previously reported response rates for Exemestane alone with this combination demonstrating a response rate (CR + PR) of 53% and a clinical benefit rate (CR + PR + SD) of 74%. By way of comparison, the efficacy of single agent Exemestane has been previously reported in randomised trials against other hormonal agents. In a trial of Exemestane *versus* megace after tamoxifen failure, single agent Exemestane demonstrated a response rate of 15% and a clinical benefit of 37.4%,[15] and as first line therapy, in a trial comparing Exemestane to tamoxifen, the response rate was 41% with a clinical benefit rate of 57%.[16]

The optimum effective dose of Celecoxib in this setting is unknown, and the dose of 400 mg twice daily was arbitrarily chosen as, in a randomised trial, it has been shown that whilst 400 mg twice daily caused significant regression of colonic adenomas, 100 mg bid was no better than placebo.[20] No comment can be made about the efficacy or toxicity of other doses of Celecoxib other than that used in here.

The major toxicities were gastrointestinal with nausea and dyspepsia occurring in 24% of patients overall, predominantly mild but sufficient for 1 patient to stop treatment. This is a higher rate of upper gastrointestinal toxicity than would be expected for Exemestane alone, but on the other hand arthralgia was less common than that previously reported.[15,16] Otherwise the combination was well tolerated. One patient, with no previous history of peptic ulceration, died of surgical complications two weeks after suffering a gastric perforation whilst on treatment. She had been on treatment for 4 months, there was no prior gastric haemorrhage and she had widespread, progressive metastatic breast cancer, including intra-abdominal disease. On balance it was concluded that this event was possibly, but not definitely, a direct consequence of her drug treatment. A second patient died of a cerebro-vascular accident. She was 79 years old, had no history of risk factors for cerebro-vascular disease and had been taking Celecoxib for 8 months. This may have been a coincidental event but an association with Celecoxib could not be excluded. The other non-malignant death on treatment was from pulmonary thromboembolism, a recognised complication of metastatic breast cancer, and was not clearly associated with either drug. No patient had a cardiac adverse event.

This is the first study to report on the combination of Exemestane and Celecoxib as first line therapy for post-menopausal women with advanced or metastatic, ER positive breast cancer. Despite the recent data on possible adverse cardiovascular effects of the COX-2 inhibitors, these results support the use of the combination of Exemestane with Celecoxib in phase III clinical trials for selected patients and patient groups. Given the concerns about longer term cardiovascular toxicity, short term, 3–4 months, neo-adjuvant therapy trials of COX2 inhibitors with aromatase inhibitors would seem the most appropriate setting.

Conflict of interest statement

This study was supported by an unrestricted academic grant from Pharmacia-Upjohn (now Pfizer).

P.A.C. has previously received consultancy and lecture fees from Pfizer.

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