Cancer Chemother Pharmacol (2008) 62:717–725
DOI 10.1007/s00280-007-0650-1

CLINICAL TRIAL REPORT

Impact of celecoxib on capecitabine tolerability and activity in pretreated metastatic breast cancer: results of a phase II study with biomarker evaluation

Alessandra Fabi · Giulio Metro · Paola Papaldo · Marcella Mottolese · Elisa Melucci · Paolo Carlini · Isabella Sperduti · Michelangelo Russillo · Alain Gelibter · Gianluigi Ferretti · Silverio Tomao · Michele Milella · Francesco Cognetti

Received: 21 September 2007 / Accepted: 20 November 2007 / Published online: 6 December 2007

Abstract
Background Preclinical evidence suggests that the cyclo-oxygenase-2 (COX-2) enzyme plays an important role in breast cancer progression. The aim of the present phase II study was to determine the activity and safety of the combination of the COX-2 inhibitor celecoxib with capecitabine in metastatic breast cancer (MBC) patients pretreated with anthracyclines and/or taxanes.
Methods Eligible patients received capecitabine 1,000 mg/m² twice daily on days 1–14 every 21 days and celecoxib 200 mg twice daily, continuously, until disease progression or unacceptable toxicity.
Results About 42 pretreated MBC patients were enrolled into the study. Median number of previous chemotherapy lines for metastatic disease was 2 (0–3). Seven patients (19%) responded to treatment while disease stabilization occurred in 17 patients (40.5%). Overall, 20 patients (47.5%) achieved clinical benefit [objective responses (CR) plus stable disease (SD) ≥6 months]. Median time to progression (TTP) and median overall survival (OS) were 5.2 and 17.8 months, respectively. Treatment was very well tolerated: grade 3 toxicities were observed in only five patients, respectively, and no grade 4 adverse events were reported. Celecoxib was never discontinued for toxicity. Analysis of COX-2 expression in the 22 patients with available tissue revealed a significantly longer TTP and OS for patients whose tumors over-expressed COX-2.
Conclusions The combination of capecitabine and celecoxib is active and safe in far advanced MBC patients. Interestingly, this association resulted in a lower-than-expected toxicity, as compared to single-agent capecitabine. The clinical relevance of COX-2 as determinant of sensitivity to treatment with celecoxib should be further evaluated in larger series of patients.

Keywords Capecitabine · Celecoxib · COX-2 · Metastatic breast cancer

A. Fabi and G. Metro contributed equally to this work.

A. Fabi · G. Metro · P. Papaldo · P. Carlini · M. Russillo · A. Gelibter · S. Tomao · F. Cognetti
Division of Medical Oncology A,
Regina Elena National Cancer Institute,
Via Elio Chianesi 53, 00144 Rome, Italy

M. Mottolese · E. Melucci
Department of Pathology,
Regina Elena National Cancer Institute,
Via Elio Chianesi 53, 00144 Rome, Italy

I. Sperduti
Division of Statistics,
Regina Elena National Cancer Institute,
Via Elio Chianesi 53, 00144 Rome, Italy

G. Ferretti · S. Tomao · M. Milella
Department of Experimental Medicine and Pathology,
University "La Sapienza", Rome, Italy

Introduction

Metastatic breast cancer (MBC) is an incurable disease whose management often includes palliative systemic chemotherapy, especially in patients with hormone receptor-negative or endocrine-resistant tumors or in patients with rapidly disseminating disease. Although recent progresses have led to an increased number of treatment options for breast cancer, best exemplified by the introduction of the anti-HER-2 drug trastuzumab as optimal standard of care for HER-2 over-expressing tumors [1], improvements in

survival of metastatic disease have been rather modest [2]. Thus, new approaches based on a deeper understanding of breast cancer biology are mandatory.

Celecoxib (Celebrex, Pfizer, New York, NY, USA) is a selective inhibitor of isoform 2 of cyclo-oxygenase (COX), the enzyme catalyzing the conversion of arachidonic acid into prostaglandins. In contrast with COX-1, which is constitutively expressed in most normal tissues, cyclo-oxygenase-2 (COX-2) is usually up-regulated in response to mitogens, growth factors, and cytokines. Preclinical evidence indicates that COX-2 products, in addition to their well-established pathophysiological role in inflammation, are also involved at multiple points throughout the tumorigenic process [3]. In fact, COX-2 is over-expressed in a variety of malignancies including breast cancer, where it has been found to associate with poor prognostic factors, such as large tumor size, high histological grade, axillary node metastases, receptor negative disease, and HER-2 amplification [4]. More recently, elevated COX-2 expression in breast cancer has also been associated with the presence of distant metastases [5]. Due to these findings, a role for COX-2 in breast carcinogenesis has been suggested and COX-2 inhibitors have been regarded as potential therapeutic agents for breast cancer. In support of this hypothesis, celecoxib has been shown to inhibit proliferation of human breast cancer cell lines [6] and, more importantly, in xenograft models of mammary tumors the administration of celecoxib led to significant regression of tumor growth in ~90% of cases [7]. Interestingly, preclinical studies have suggested that the addition of celecoxib to standard cytotoxics may enhance the effects of several anticancer agents [8], especially 5-fluorouracil (5-FU) [9]. In clinical trials it has been demonstrated that celecoxib administered concomitantly with infusional 5-FU does not increase the expected toxicities of 5-FU alone [10, 11]. Of note, a retrospective evaluation of metastatic colorectal cancer patients treated with capecitabine and celecoxib given for pain indications, suggested that celecoxib may not only improve anti-tumor activity but also attenuate two major capecitabine-related adverse events, namely hand-foot syndrome (palmar-erythrodysestesia, HFS) and diarrhea [12, 13].

Capecitabine (Xeloda, Hoffman-LaRoche Inc., Nutley, NJ, USA), a fluoropyrimidine carbamate, is an orally administered pro-drug which is converted into the active compound 5-FU through a three-stage enzymatic process. Capecitabine unique mechanism of action allows delivery of 5-FU preferentially to the tumor, since thymidine phosphorylase, the enzyme responsible for the final conversion step, is predominantly localized within tumor tissue [14]. Prospective clinical studies of single agent capecitabine established a role for this agent in MBC patients pretreated with anthracyclines and/or taxanes [15–18]. However, at the standard dosage of 2,500 mg/m² daily for 14 days every 3 weeks, dose reduction due to development of treatment-related toxicity, mainly HFS, and diarrhea, was a common event, being required in 37–50% of patients [16–18]. Interestingly, in one of the pivotal trial of capecitabine monotherapy it was showed that a side effect-driven dose reduction to 2,000 mg/m² does not compromise the efficacy of treatment [16], suggesting that a starting lower dose of 2,000 mg/m² can provide equal benefit because of its superior therapeuthic index [19, 20].

Based on these data we designed a phase II study in order to investigate the clinical activity and tolerability of capecitabine combined with celecoxib (CapCel) in MBC patients previously treated with anthracyclines and/or taxanes.

Materials and methods

Study design and treatment

Primary end-points of this mono-institutional, open-label, single-arm phase II study were to determine the time to progression (TTP) and the safety of CapCel, while secondary objectives were response rates and overall survival (OS).

The trial was conducted in full agreement with the Declaration of Helsinki and International Committee on Harmonization guidelines for good clinical practice. Before initiation, the study protocol was approved by the local ethics committee. Written informed consent was obtained from all patients prior to study enrollment.

Capecitabine was administered orally in two daily doses within 30 min after breakfast and dinner at the dose of 1,000 mg/m² twice daily for 14 days every 21 days starting on day one. Celecoxib was administered at the dose of 200 mg twice daily, orally with food, starting on day 1, throughout the treatment and rest periods. One cycle of therapy consisted of 3 weeks of treatment. Prophylactic oral proton-pump inhibitors (20 mg/d) were administered to all patients starting on day one.

Study drugs were continued until disease progression, unacceptable toxicity, or patient withdrawal.

Eligibility criteria

The study population included female patients with histologically or cytologically confirmed breast cancer and disease recurrence during or following treatment with anthracyclines- and/or taxanes-including regimens. No restriction was made on the basis of the number of prior chemotherapeutic lines and/or endocrine therapies received as well as radiotherapy provided that at least 4 weeks had elapsed since last treatment. Patients with

HER-2-positive [3+ protein expression by immunohistochemistry (IHC) or gene amplification by fluorescence in situ hybridization] tumors were eligible for the study if progressing following at least one prior trastuzumab-based regimen for metastatic disease. Previous exposure to 5-FU was not considered an exclusion criterion, with the exception of prior history of severe and unexpected reaction to fluoropyrimidine therapy (with or without documented dihydropyrimidine dehydrogenase deficiency) or hypersensitivity to 5-FU. To be eligible for the study, patients were also required to have evaluable and/or bidimensionally measurable disease in at least one site that was outside a previously irradiated area. The following were the other eligibility criteria: age $\geq$18 years, Eastern Cooperative Oncology Group performance status (PS) $\leq$2, estimated life expectancy of at least 12 weeks and adequate renal, hepatic, and hematologic function. Patients who were not able to swallow intact capecitabine and celecoxib capsules were excluded from the study, as were those with malabsorption syndromes or other conditions that could potentially impair absorption of study medications. The presence of clinically significant cardiovascular disorders including angina pectoris, history of congestive heart failure, myocardial infarction, and cerebrovascular events precluded participation to the current study. Patients were also excluded if they had history of allergy to sulfa drugs or any other non-steroidal anti-inflammatory drugs (NSAIDs) or were on continuous therapy with NSAIDs for more than 30 days before enrollment. While on study, patients were instructed to avoid any NSAIDs other than the study drug celecoxib (low-dose aspirin $\leq$325 mg/day allowed). Documented active peptic ulcer, history of gastrointestinal hemorrhage, symptomatic and/or uncontrolled brain metastases, concomitant therapy with oral anti-coagulants, previous diagnosis of other malignancy within 5 years of study enrollment, with the exception of in situ carcinoma of the cervix and adequately treated non-melanoma skin malignancies, were among other exclusion criteria. Pregnant or nursing women and those with reproductive potential not using an effective contraceptive method were excluded from the study.

Safety and response assessment

Pretreatment evaluation included a medical history and clinical examination, hematology, and blood chemistry (performed within 7 days before treatment start), ECG, chest X-rays, and tumor measurement based on standard radiologic methods or physical examination. During the treatment period, hematology, and blood chemistry were performed every cycle. Safety was evaluated in all patients who received at least one dose of study drugs. All adverse events (including alterations in laboratory parameters) considered to be possibly, probably or definitely related to study treatment were graded 1–4 according to NCI-CTCAEv3 [21]. Hand-foot syndrome was graded 1–3 as defined in a previous trial of capecitabine [15]. In case of capecitabine-related adverse events greater or equal than grade 2, the standard dose modification scheme of capecitabine, described in detail by Blum et al. [15], was applied. Celecoxib, but not capecitabine was discontinued in case of gastrointestinal bleeding or gastric/duodenal erosion or ulcer documented at esophagogastroduodenoscopy (EGDS).

Patients who received at least one cycle of treatment were evaluable for efficacy. Tumor assessments were performed every three cycles according to standard WHO criteria [22]. Objective responses (CR or PR) had to be confirmed for a minimum of 4 weeks after they were first observed. Clinical benefit was defined as the sum of CR or PR plus stable disease (SD) $\geq$6 months. For patients achieving a PR, duration of response was defined as the time elapsing between the first day of treatment and the date of observation of PD. TTP was calculated from the start of treatment to the date of objective evidence of progressive disease or death of the patient in the absence of documented disease progression. OS was estimated from the day of first treatment administration to the date of the death of the patient due to any cause. Survival data were collected every 2 months after patients went off study.

COX-2 analysis

Sections from paraffin-embedded tissue blocks containing representative malignant cells obtained at the time of diagnosis of primary breast cancer were used for this analysis. Briefly, 5-μm-thick sections were pretreated in a thermostatic bath at 96°C for 40 min in 10-mM-citrate buffer (pH6) and incubated with COX-2 polyclonal antibody (pAb, Cayman Chemical Co., SIAL, Rome, Italy; 125 ng/μl) for 60 min at room temperature The immunoreactions were revealed using the Super Sensitive Link-Label IHC Detection System (BioGenex, Space, Milan, Italy) employing 3-amino-9-ethylcarbazole (AEC substrate chromogen, Dako, Glostrup, Denmark) as chromogenic substrate. All sections were slightly counterstained with Mayer's Haematoxylin and mounted in aqueous mounting medium (Glycergel, Dako). Immunohistochemical staining was performed at the Pathology Department of the Regina Elena National Cancer Institute and the slides were interpreted by one investigator (M.M.), who was blinded to all patient information.

For analytic purposes the scoring system previously described by Ristimaki et al. was used to evaluate COX-2 expression [4] (Fig. 1a, b).

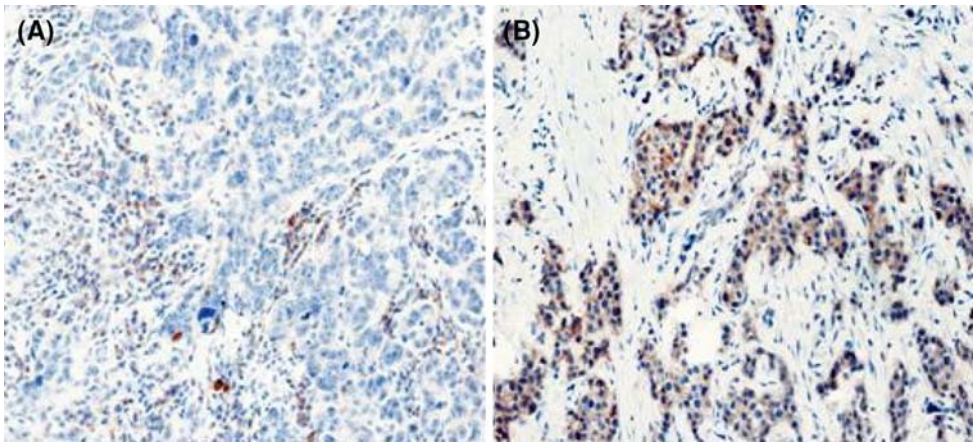

Fig. 1 Examples of immunohistochemical expression of COX-2 (original amplification ×20). COX-2 stained either as negative (a) or positive (b)

Statistical considerations

A single stage phase II design proposed by A'Hern [23] was employed. Assuming that the hypothesis of interest was a 3-month progression-free survival of 60%, and wishing to exclude from further evaluation treatment with a progression-free survival of 40%, a total of 24 of 42 patients free from progression at 3 months had to be observed. These figures ensured a significance level of 0.05 at a power of 80%. Data were analyzed according to the intent-to-treat (ITT) principles and reported with the 95% confidence intervals. Time to events was estimated with the Kaplan-Meier method. The Cox proportional-hazard model was used to identify independent prognostic factors of survival.

Results

Patients characteristics

Forty-two women were enrolled into the trial between February 2004 and December 2006. All patients were evaluable for safety and activity. Patient characteristics are listed in Table 1. The median age was 57 years (range 33–82), and nearly half of the patients ($n = 19$, 45%) had an ECOG PS of 0 (range 0–2). The majority of patients ($n = 31$, 73.5%) had visceral disease as predominant metastatic localization, with ten patients (24%) suffering from asymptomatic brain metastases. All patients had received prior anthracycline-containing chemotherapy. Thirty-three patients (78.5%) had also received prior chemotherapy with taxanes. The median number of previous chemotherapy lines received for metastatic disease was 2 (range 0–3). The four patients who were treated with first-line chemotherapy had been exposed to both anthracyclines and taxanes in the adjuvant setting.

Table 1 Characteristics of patients

Total number of patients	42
Age, median years (range)	57 (33–82)
ECOG performance status	
0	19 (45%)
1	17 (40.5%)
2	6 (14.5%)
Receptor status	
ER and/or PgR positive	26 (62%)
ER and PgR negative	12 (28.5)
Unknown	4 (9.5%)
HER-2 expression by IHC	
HER-2 negative	24 (57%)
HER-2 2+ and FISH positive	5 (12%)
HER-2 3+	6 (14.5%)
Unknown	7 (16.5%)
Up-front metastatic presentation	6 (14.5%)
Predominant metastatic sites	
Liver	20 (47.5%)
Lung	11 (26%)
Bone	10 (24%)
Soft tissues	1 (2.5%)
Brain involvement	10 (24%)
Prior exposure to anthracyclines	42 (100%)
Anthracyclines in the neoadjuvant/adjuvant setting	23 (55%)
Anthracyclines in the metastatic setting	19 (45%)
Prior exposure to taxanes	33 (78.5%)
Prior chemotherapy lines for metastatic disease	38 (90.5%)
0	4 (9.5%)
1	13 (31%)
2	17 (40.5%)
3	8 (19%)
Median number of prior chemotherapy lines for metastatic disease (range)	2 (0–3)

ER estrogen receptor, *FISH* fluorescence in situ hybridization, *IHC* immunohistochemistry, *PgR* progesterone receptor

Table 2 Activity of the capecitabine and celecoxib combination

Total number of patients	42
Complete response	0
Partial response	8 (19%) (95% CI 7.2–30.9)
Stable disease ≥6 months	12 (28.5%)
Stable disease <6 months	5 (12%)
Progressive disease	17 (40.5%)

Anti-tumor activity

Table 2 shows the activity of the CapCel combination. In the ITT analysis, eight patients (19%) obtained a PR (95% CI 7.2–30.9), while a further 17 patients achieved disease stabilization (40.5%). Twenty patients (47.5%) experienced a clinical benefit. The median duration of response was 13 months (95% CI 12–14) and median TTP was 5.2 months (95% CI 2.9–7.5) (Fig. 2a). At 3 months 29 of 42 patients (69%) were free from progression and the 6- and 12-month progression-free survival rates were 43.6 and 25.7%, respectively. At a median follow up of 15 months (range 2–28) median OS was 17.8 months (95% CI 12.2–23.3) (Fig. 2b) and the corresponding 1- and 2-year survival rates were 62.3 and 31.1%, respectively. Tables 3 and 4 show the results of univariate and multivariate analysis of TTP and OS. In the multivariate analysis a poor PS (1–2 vs. 0), no response to therapy and younger age (<50 years) were independent prognostic factors for shorter TTP, while only poor PS was an independent prognostic factor for OS.

Safety

Patients received a total of 306 cycles throughout the study with a median of six cycles (range 2–18) per patient. Treatment-related adverse events (all grades, maximum toxicity per patient reported) are summarized in Table 5. The majority of treatment-related adverse events were mild (grade 1) or moderate (grade 2) in intensity. The predominant grade 2 treatment-related toxicities were, in decreasing order of frequency, HFS (14.5%), neutropenia (12%), and diarrhea (9.5%). Two patients experienced grade 2 heartburn, with no signs or symptoms of gastrointestinal bleeding or EGDS-documentation of active peptic ulcer/erosion or hemorrhage of the upper gastrointestinal tract. Both patients promptly recovered after increasing the daily dose of oral proton-pump inhibitors to 40 mg/day. None of the patients discontinued celecoxib due to toxicity.

Only five grade 3 adverse events were observed, consisting of HFS, mucositis, nail changes, neutropenia, and

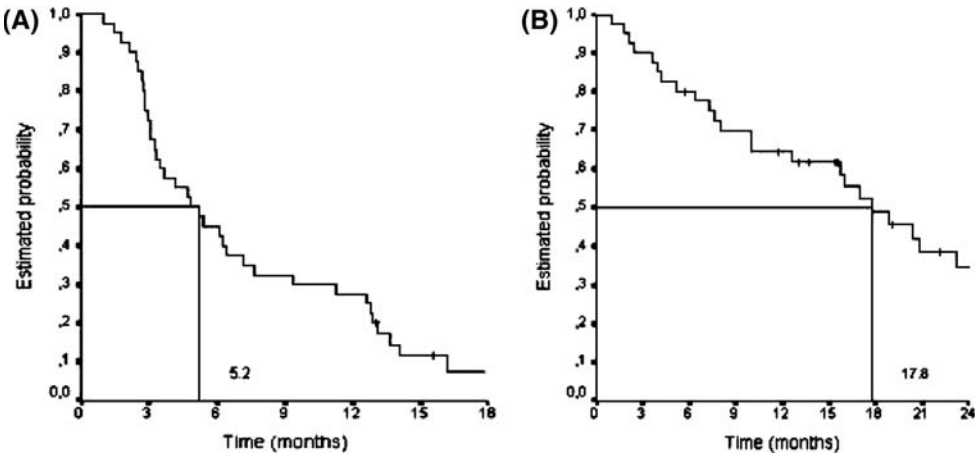

Fig. 2 Time to progression (a) and overall survival (b) in the intention-to-treat analysis

Table 3 Univariate and multivariate analysis of time to progression

TTP	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (<50 vs. ≥50)	2.31 (1.13–4.75)	0.02	3.10 (1.41–6.80)	0.005
Performance status (1–2 vs. 0)	2.11 (1.08–4.12)	0.03	2.10 (1.01–4.39)	0.05
Pretreatment with Taxanes (yes versus no)	2.20 (0.95–5.07)	0.07		
Adjuvant anthracyclines (yes versus no)	1.01 (0.51–2.01)	0.99		
Predominant metastatic site (visceral versus non-visceral)	1.78 (0.78–4.05)	0.17		
Capecitabine treatment (>2 lines vs. ≤2 lines)	1.56 (0.79–3.07)	0.20		
Response to treatment (no versus yes)	3.32 (1.27–8.65)	0.01	2.71 (1.00–7.33)	0.05

HR and CI can only be calculated for two variables

CI confidence interval, *HR* hazard ratio, *TTP* time to progression

Table 4 Univariate and multivariate analysis of overall survival

OS	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (<50 vs. ≥50)	1.40 (0.62–3.15)	0.42		
Performance status (1–2 vs. 0)	2.17 (1.00–4.84)	0.05	2.17 (1.00–4.84)	0.05
Pretreatment with Taxanes (yes versus no)	1.26 (0.42–3.80)	0.68		
Adjuvant anthracyclines (yes versus no)	1.02 (0.46–2.28)	0.96		
Predominant metastatic site (visceral versus non-visceral)	1.01 (0.40–2.54)	0.98		
Capecitabine treatment (>2 lines vs. ≤2 lines)	1.07 (0.46–2.50)	0.88		
Response to treatment (no versus yes)	3.58 (0.84–15.18)	0.08		

HR and CI can only be calculated for two variables

CI confidence interval, *HR* hazard ratio, *OS* overall survival

Table 5 Summary of treatment-related adverse events

Laboratory parameter	Number of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Leucopenia	8 (19%)	3 (7%)	0	0
Neutropenia	6 (14.5%)	5 (12%)	1 (2.5%)	0
Anemia	10 (24%)	2 (5%)	1 (2.5%)	0
Thrombocytopenia	1 (2.5%)	0	0	0
Hyperbilirubinemia	2 (5%)	2 (5%)	0	0
AST and/or ALT elevation	5 (12%)	1 (2.5%)	0	0
Non-hematological	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	7 (16.5%)	3 (7%)	0	0
Mucositis	6 (14.5%)	0	1 (2.5%)	0
Diarrhea	6 (14.5%)	4 (9.5%)	0	0
Hand-foot syndrome	6 (14.5%)	6 (14.5%)	1 (2.5%)	–
Sensory/motor neuropaty	3 (7%)	0	0	0
Erythematous rash	2 (5%)	1 (2.5%)	0	0
Nail changes	3 (7%)	3 (7%)	1 (2.5%)	–
Heartburn/dyspepsia	6 (14.5%)	2 (5%)	0	–
Fatigue	5 (12%)	3 (7%)	0	0

anemia. The latter condition occurred in a heavily pretreated patient who had also been extensively irradiated for bone metastases. In view of the fact that anemia was present prior to study entry and that hemoglobin levels were stable after an initial worsening (from grades 2 to 3 after cycle 1), also considering that no signs or symptoms of active bleeding were present, this patient was managed conservatively with intensive hematologic monitoring and without red blood cell transfusion. No treatment-related grade 4 toxicities were observed and no cardiovascular events or deaths were reported as being related to the study medications. Treatment was discontinued due to toxicity in only one patient (grade 3 mucositis occurring after two cycles).

The dose of capecitabine was reduced to 75% of the starting dose in ten patients (24%). The adverse events leading to dose reduction were HFS (five patients), laboratory abnormalities (hyperbilirubinemia and elevation of transaminases in one patient each), mucositis, diarrhea, and neutropenia (one patient each, respectively). The median time to first dose reduction and HFS onset was 3 months, corresponding to the fourth treatment cycle. The mean delivered dose intensity of capecitabine was 634 mg/m^2/wk (planned 667 mg/m^2/wk) corresponding to 95% of the planned dose intensity.

Outcome according to COX-2 expression

Cyclo-oxygenase-2 expression was successfully evaluated in tumors from 22 individuals. According to the scoring system adopted, COX-2 positivity was observed in 12 patients (54.5%). Among the 22 patients evaluated for COX-2 expression, CB was achieved in 11 patients, eight of whom resulted COX-2 positive (73%). Patients with COX-2 positive tumors had a significantly longer TTP than COX-2 negative patients (5.4 months vs. 3.1 months, $P = 0.04$). Median OS also significantly favored COX-2 positive patients compared to COX-2 negative ones (27.9 months vs. 7.6 months, $P = 0.02$) (Fig. 3a–b).

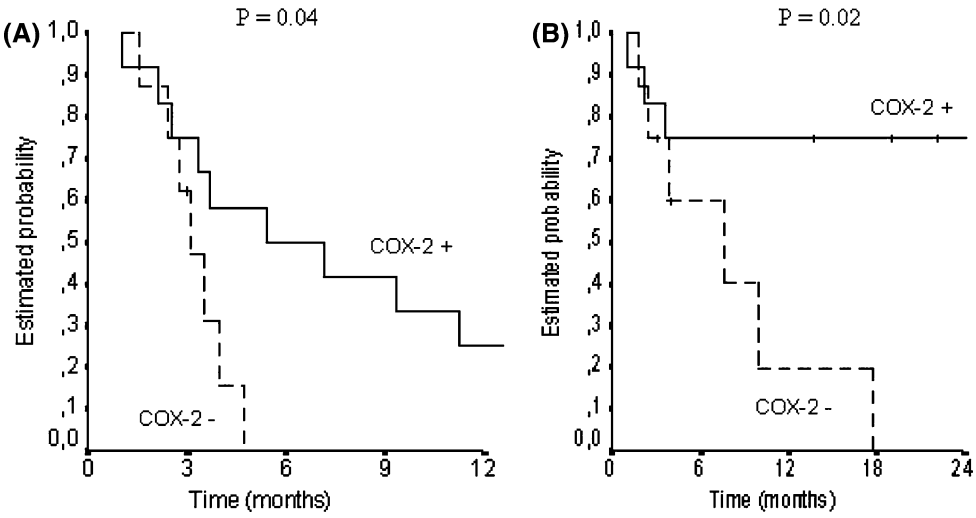

Fig. 3 Time to progression (**a**) and overall survival (**b**) according to COX-2 expression (22 patients)

Discussion

To our knowledge, this is the first clinical study evaluating the combination of chemotherapy, namely capecitabine, with celecoxib in MBC. Previous experience of celecoxib and chemotherapy in breast cancer refers to the neoadjuvant setting, where celecoxib appeared to increase the response rate observed with chemotherapy alone by approximately to 20% [24]. Although limited to a small series of patients, clinical experience and the preclinical evidence of the potentiating effects of celecoxib on chemotherapy [8, 9] provided a strong rationale to evaluate whether an enhancement of the clinical activity of chemotherapy would also be observed in the metastatic setting.

The response rate of 19% achieved with CapCel in the present study is not inferior to that of phase II studies of capecitabine monotherapy where response rates ranging from 15 to 28% were observed in anthracycline- and taxane-pretreated MBC patients [15–18]. Of note, CapCel therapy achieved a median TTP of 5.2 months and a median OS of 17.8 months. These results should be regarded as very interesting, especially when considering that they were obtained in a heavily pretreated population with unfavorable prognostic factors, such as the presence of visceral and brain metastases in approximately three-quarters and one-quarter of cases, respectively. Moreover, such results compare favourably with those reported in the literature by prospective studies of single-agent capecitabine, where median TTP ranges from 3 to 4.9 months and median OS ranges from 10.1 to 15.2 months [15–18]. This study also confirms the clinical data in support of the use of a lower starting dose of capecitabine (2,000 mg/m²) because of its preserved efficacy and lower toxicity [16, 19, 20].

In the present study, celecoxib was administered at 200 mg twice daily based on a previous experience from our group, where celecoxib at the dose of 200 mg twice daily in combination with infusional 5-FU as second-line therapy for advanced pancreatic cancer was associated with a 18% of early treatment discontinuation due to the development of gastrointestinal toxicity (two cases of EGDS-documented duodenal ulcer and one grade 2 heartburn) [10]. Moreover, chemoprevention trials conducted in colorectal cancer suggested no difference in efficacy between the 200 and 400-mg twice-daily dose of celecoxib [25]. However, it is presently unclear whether greater anti-tumor activity would be achieved in advanced cancer patients by increasing the dose of this experimental drug. On the other hand, trials on the use of celecoxib as chemopreventive agent have also suggested that patients on continuous treatment with celecoxib are at increased risk of developing cardiovascular events [26]. In the present study no cardiovascular events were reported, indicating that short-term use of celecoxib in MBC has a good safety profile in terms of cardiac toxicity. Remarkably, celecoxib in combination with capecitabine also showed good gastrointestinal tolerability, since the only two patients developed grade 2 heartburn (with no documentation of ulcer at EGDS) and both recovered promptly after increasing therapy with proton-pump inhibitors without discontinuation of celecoxib.

Overall, the CapCel combination proved extremely safe in this population of pretreated MBC patients. Grade 3 adverse events were observed in only five patients and were easily manageable with treatment delays and/or capecitabine dose reductions. No grade 4 toxicities were reported and only one patient (2.5%) underwent early treatment discontinuation due to toxicity. Interestingly, retrospective clinical data suggest that celecoxib, by inhibiting COX-2-mediated inflammation, might attenuate or even prevent two peculiar capecitabine-related side effects potentially due to COX-2 activation such as HFS and diarrhea [12, 13]. Although this trial was not designed to answer this question, it is interesting to note that CapCel was associated

with a low occurrence of both HFS and diarrhea, as compared to historical data coming from prospective studies of single agent capecitabine [15–18, 27–29]. Although the starting dose of capecitabine was higher (2,500 or 2,510 mg/m²/die) in most of these studies, we cannot rule out that the low incidence of capecitabine-related HFS and diarrhea observed in our study might be due to the concomitant administration of celecoxib. This hypothesis is supported by the retrospective evidence that a lower capecitabine starting dose (2,000 mg/m²/die) is still associated with a 14 and 6% incidence of grade 3/4 HFS and diarrhea, respectively, even in chemonaïve MBC patients [30].

In a subset analysis of 22 patients who had primary tissue available for analysis, significantly longer TTP and OS were observed for COX-2 positive patients, as compared to COX-2 negative ones. Although limited by the small number of patients on which this analysis was carried out, the favorable outcome observed in COX-2 positive patients should be regarded as a relevant finding and supports COX-2 evaluation as a potential biomarker of sensitivity to celecoxib. In fact, COX-2 over-expression might predict response to treatment, as it has been recently shown for aspirin in the chemoprevention of colorectal cancer [31].

In conclusion, this study shows that capecitabine in combination with celecoxib is an active regimen for pretreated MBC patients resulting in a 47.5% of CB in a poor-prognosis population. Our results also indicate that this association has a very manageable toxicity profile, which compares favorably with that expected with single-agent capecitabine, thus corroborating retrospective data coming from studies on metastatic colorectal cancer patients on the potential role that celecoxib might play in lessening or even preventing capecitabine-related HFS and diarrhea. Only the ongoing National Cancer Institute randomized phase III study comparing celecoxib versus placebo in patients with advanced colorectal and breast cancers will lead to conclusive results on the true impact of celecoxib on capecitebine-related adverse events [32]. Finally, the improved clinical outcome observed in patients with COX-2 positive tumors supports the inclusion of tissue evaluation of COX-2 expression in future clinical trials of celecoxib given as anti-cancer therapy.

Acknowledgments This work was supported in part by the Italian Association for Cancer Research (AIRC grants to MM) and by the Italian Ministry of Health (grants to AF and MM).

References

1. Demonty G, Bernard-Marty C, Puglisi F, Mancini I, Piccart M (2007) Progress and new standards of care in the management of HER-2 positive breast cancer. Eur J Cancer 43:497–509
2. Abrial C, Leheurteur M, Cabrespine A, Mouret-Reynier MA, Durando X, Ferriere JP, Kwiatkowski F, Penault-Llorca F, Cure H, Chollet P (2006) Does survival increase in metastatic breast cancer with recently available anticancer drugs? Oncol Res 15:431–439
3. Cao Y, Prescott SM (2002) Many actions of cyclooxygenase-2 in cellular dynamics and in cancer. J Cell Physiol 190:279–286
4. Ristimaki A, Sivula A, Lundin J, Lundin M, Salminen T, Haglund C, Joensuu H, Isola J (2002) Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. Cancer Res 62:632–635
5. Ranger GS, Thomas V, Jewell A, Mokbel K (2004) Elevated cyclooxygenase-2 expression correlates with distant metastases in breast cancer. Anticancer Res 24:2349–2351
6. Arun B, Zhang H, Mirza NQ (2001) Growth inhibition of breast cancer cells by celecoxib. Breast Cancer Res Treat 69:234a
7. Alshafie GA, Abou-Issa HM, Seibert K, Harris RE (2000) Chemotherapeutic evaluation of celecoxib, a cyclooxygenase-2 inhibitor, in a ratmammary tumor model. Oncol Rep 7:1377–1381
8. Hida T, Kozaki K, Ito H Miyaishi O, Tatematsu Y, Suzuki T, Matsuo K, Sugiura T, Ogawa M, Takahashi T, Takahashi T (2002) Significant growth inhibition of human lung cancer cells both in vitro and in vivo by the combined use of a selective cyclooxygenase 2 inhibitor, JTE-522, and conventional anticancer agents. Clin Cancer Res 8:2443–2447
9. Irie T, Tsujii M, Tsuji S Yoshio T, Ishii S, Shinzaki S, Egawa S, Kakiuchi Y, Nishida T, Yasumaru M, Iijima H, Murata H, Takehara T, Kawano S, Hayashi N (2007) Synergistic antitumor effects of celecoxib with 5 fluorouracil depend on IFN-gamma. Int J Cancer 121:878–883
10. Milella M, Gelibter A, Di Cosimo S, Bria E, Ruggeri EM, Carlini P, Malaguti P, Pellicciotta M, Terzoli E, Cognetti F (2004) Pilot study of celecoxib and infusional 5-fluorouracil as second-line treatment for advanced pancreatic carcinoma. Cancer 101:133–138
11. Blanke CD, Mattek NC, Deloughery TG, Koop DR (2005) A phase I study of 5-fluorouracil, leucovorin, and celecoxib in patients with incurable colorectal cancer. Prostaglandins Other Lipid Mediat 75:169–172
12. Lin E, Morris JS, Ayers GD (2002) Effect of celecoxib on capecitabine-induced hand-foot syndrome and antitumor activity. Oncology (Williston Park) 16(suppl 14):31–37
13. Lin EH, Curley SA, Crane CC, Feig B, Skibber J, Delcos M, Vadhan SR, Morris J, Ayers GD, Ross A, Brown T, Rodriguez-Bigas MA, Janjan N (2006) Retrospective study of capecitabine and celecoxib in metastatic colorectal cancer: potential benefits and COX-2 as the common mediator in pain, toxicities and survival? Am J Clin Oncol 29:232–239
14. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I, Ishitsuka H (1998) Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274–1281
15. Blum JL, Jones SE, Buzdar AU, Lo Russo PM, Kuter I, Vogel C, Osterwalder B, Burger HU, Brown CS, Griffin T (1999) Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 17:485–493
16. Blum JL, Dieras V, Lo Russo PM, Horton J, Rutman O, Buzdar A, Osterwalder B (2001) Multicenter, phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. Cancer 92:1759–1768
17. Reichardt P, Von Minckwitz G, Thuss-Patience PC, Jonat W, Kolbl H, Janicke F, Kieback DG, Kuhn W, Schindler AE, Mohrmann S, Kaufmann M, Luck HJ (2003) Multicenter phase II study of oral capecitabine (Xeloda(“)) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy. Ann Oncol 14:1227–1233
18. Fumoleau P, Largillier R, Clippe C, Dièras V, Orfeuvre H, Lesimple T, Culine S, Audhuy B, Serin D, Curé H, Vuillemin E,

Morère JF, Montestruc F, Mouri Z, Namer M (2004) Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer 40:536–542
19. Bajetta E, Procopio G, Celio L, Gattinoni L, Della Torre S, Mariani L, Catena L, Ricotta R, Longarini R, Zilembo N, Buzzoni R (2005) Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol 23:2155–2161
20. Hennessy BT, Gauthier AM, Michaud LB, Hortobagyi G, Valero V (2005) Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: retrospective analysis of patients treated at M. D. Anderson Cancer Center and a review of capecitabine toxicity in the literature. Ann Oncol 16:1289–1296
21. National Cancer Institute (2007) Common toxicity criteria version 3.0. Available from URL: http://ctep.cancer.gov/forms/CTCAEv3.pdf [accessed June 9, 2007]
22. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214
23. A'Hern RP (2001) Sample size tables for exact single-stage phase II designs. Stat Med 20:859–866
24. Chow LW, Loo WT, Toi M (2005) Current directions for COX-2 inhibition in breast cancer. Biomed Pharmacother 59(Suppl 2):281–284
25. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, Tang J, Rosenstein RB, Wittes J, Corle D, Hess TM, Woloj GM, Boisserie F, Anderson WF, Viner JL, Bagheri D, Burn J, Chung DC, Dewar T, Foley TR, Hoffman N, Macrae F, Pruitt RE, Saltzman JR, Salzberg B, Sylwestrowicz T, Gordon GB, Hawk ET, APC Study Investigators (2006) Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 355:873–884
26. Psaty BM, Potter JD (2006) Risks and benefits of celecoxib to prevent recurrent adenomas. N Engl J Med 355:950–952
27. O'Shaughnessy JA, Blum J, Moiseyenko V, Jones SE, Miles D, Bell D, Rosso R, Mauriac L, Osterwalder B, Burger HU, Laws S (2001) Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol 12:1247–1254
28. Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, Dickler M, Overmoyer BA, Reimann JD, Sing AP, Langmuir V, Rugo HS (2005) Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 23:792–799
29. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, Jagiello-Gruszfeld A, Crown J, Chan A, Kaufman B, Skarlos D, Campone M, Davidson N, Berger M, Oliva C, Rubin SD, Stein S, Cameron D (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355:2733–2743
30. Yap YS, Kendall A, Walsh G, Banerji U, Johnston SR, Smith IE, O'brien M (2007) Clinical efficacy of capecitabine as first-line chemotherapy in metastatic breast cancer-How low can you go? Breast 16:420–424
31. Chan AT, Ogino S, Fuchs CS (2007) Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 356:2131–2142
32. National Cancer Institute (2007) ClinicalTrials.gov. Available from URL: http://clinicaltrials.gov/ct/show/NCT00305643?order=1 [Accessed June 9, 2007]