Cancer Chemother Pharmacol (2010) 65:457–465
DOI 10.1007/s00280-009-1049-y

ORIGINAL ARTICLE

Sequential administration of dose-dense epirubicin/cyclophosphamide followed by docetaxel/capecitabine for patients with HER2-negative and locally advanced or node-positive breast cancer

Yago Nieto · José Manuel Aramendía · Jaime Espinós · Susana De la Cruz · Oscar Fernández-Hidalgo · Marta Santisteban · Leyre Arbea · Javier Aristu · Rafael Martínez-Monge · Marta Moreno · Luis Pina · Josu Sola · Gerardo Zornoza · Fernando Martínez Regueira

Received: 8 May 2009 / Accepted: 1 June 2009 / Published online: 14 June 2009

Abstract
Purpose Capecitabine is effective against metastatic breast cancer (MBC). We hypothesized that sequential treatment with dose-dense epirubicin/cyclophosphamide (EC) and docetaxel/capecitabine would be active and tolerable in the adjuvant/neoadjuvant setting.
Methods In this prospective phase II clinical trial patients with HER2-negative and node-positive or locally advanced tumors were eligible to receive four cycles of EC (100/600 mg/m^2) every 2 weeks with G-CSF on days 3–10, followed by four cycles of docetaxel/capecitabine (75/1,000 mg/m^2 b.i.d., days 1–14) every 3 weeks.
Results Fifty-five patients were enrolled with median age of 49, and 80% had hormone receptor-positive disease. The median tumor size was 2.5 cm, with a median of two axillary nodes involved. Seventy-five percent of the first 20 patients had grade 2/3 hand-foot syndrome (HFS). Dose reduction of capecitabine to 800 mg/m^2 reduced the grade 2/3 HFS incidence to 31% in the remaining patients. No grade 4/5 toxicities were observed. All 20 patients treated preoperatively responded, with 5 (25%) pathologic complete responses and 3 additional pT_0N_1 tumors. At a median follow-up of 48 (range 28–60) months, the event-free and overall survival rates are 91 and 98%, respectively.
Conclusions Sequential treatment with dose-dense EC followed by docetaxel/capecitabine, using a lower capecitabine dose than that approved for MBC, has an acceptable toxicity profile and encouraging activity when used as neoadjuvant or adjuvant treatment of breast cancer.

Keywords Phase II trial · Capecitabine · Docetaxel · Adjuvant · Neoadjuvant · Breast cancer

Y. Nieto · J. M. Aramendía · J. Espinós · S. De la Cruz · O. Fernández-Hidalgo · M. Santisteban
Department of Medical Oncology,
Clínica Universitaria de Navarra, Pamplona, Spain

L. Arbea · J. Aristu · R. Martínez-Monge · M. Moreno
Department of Radiation Oncology,
Clínica Universitaria de Navarra, Pamplona, Spain

L. Pina
Department of Radiology,
Clínica Universitaria de Navarra, Pamplona, Spain

J. Sola
Department of Pathology,
Clínica Universitaria de Navarra, Pamplona, Spain

G. Zornoza · F. M. Regueira
Department of Breast Surgery,
Clínica Universitaria de Navarra, Pamplona, Spain

Y. Nieto (✉)
UT MD Anderson Cancer Center, 1515 Holcombe Blvd,
Unit 423, Houston, TX 77030, USA
e-mail: ynieto@mdanderson.org

Introduction

Recent advances in the treatment of node-positive breast cancer include the development of dose-dense anthracyline schemas [1] and combinations of anthracyclines and taxanes. Several trials have shown the benefit of both sequential and concurrent combinations of anthracyclines and paclitaxel or docetaxel [2–6].

Capecitabine is an effective agent in metastatic breast cancer (MBC). O'Shaughnessy and colleagues have shown the superiority of docetaxel/capecitabine over docetaxel alone in patients with metastatic disease [7]. The synergy

between these two agents seems to result from docetaxel-induced upregulation in tumor cells of thymidine phosphorylase (TP) [8, 9], the enzyme responsible for the intracellular activation of capecitabine from its intermediate metabolite 5′-deoxy-5-fluorouridine (5′-FUDR) to the active form 5-fluorouracil (5-FU). Numerous studies have demonstrated that higher TP content in tumor cells has a favorable effect on patient outcomes after treatment with capecitabine [10–13].

In view of its effectiveness in metastatic disease, capecitabine holds substantial promise in the treatment of nonmetastatic breast cancer, a setting where it has not been studied extensively. Prior treatment with doxorubicin/cyclophosphamide (AC) or epirubicin/cyclophosphamide (EC), but not with a 5-FU-containing regimen, has been shown to upregulate the expression of TP in breast cancer cells [14]. We hypothesized that sequential treatment with TP-upregulating dose-dense epirubicin/cyclophosphamide (EC) followed by docetaxel/capecitabine would be active and well tolerated in the adjuvant or neoadjuvant settings. Given the observed antagonism between the anti-HER2 antibody trastuzumab and 5-FU (and, by extension, capecitabine) in preclinical studies [15, 16], we restricted enrollment to patients with HER2-negative disease, who do not benefit from trastuzumab.

We report here a prospective phase II study of four cycles of dose-dense EC followed by four cycles of docetaxel/capecitabine as adjuvant or neoadjuvant treatment of patients with HER2-negative, node-positive or locally advanced breast cancer.

Patients and methods

This trial was conducted at the Clinica Universitaria de Navarra, Spain, between 2005 and 2006. The study protocol was approved by the Ethics Committee of our institution. All patients gave informed consent prior to enrollment. Eligible patients were 18–70 years of age and had histologically proven breast cancer, stage IIA to IIIC, with either involvement of axillary nodes or locally advanced disease that was deemed suitable for preoperative chemotherapy; performance status 0–2; normal end-organ function (creatinine clearance >50 ml/min, left ventricle ejection fraction >50%, glutamic oxaloacetic transaminase (GOT, AST)/glutamic pyruvic transaminase (GPT, ALT)/bilirubin <2× upper limit of normal, and normal peripheral blood counts); and HER2-negative tumors (0 or 1+ by immunohistochemistry or negative by fluorescence in situ hybridization). Exclusion criteria were pregnancy, presence of metastases, and previous chemotherapy.

The study endpoints were: (1) to define the hematologic and nonhematologic toxicities of the proposed sequential regimen as adjuvant or neoadjuvant treatment, (2) to assess the event-free survival (EFS) and overall survival (OS) of the study population after this treatment, and (3) to determine the clinical response rate and pathological complete response (pCR) rate in the subset of patients treated preoperatively.

Treatment plan

Surgery of the primary tumor consisted of modified radical mastectomy or lumpectomy, with or without sentinel lymph node biopsy. Adjuvant chemotherapy was to start within 6 weeks following surgery. Pretreatment workup included a complete blood count with differential, chemical profile (creatinine, urea, lactate dehydrogenase, bilirubin, alkaline phosphatase, transaminases), chest X-ray, liver ultrasonography or abdominal computed tomography, bone scan, tumor markers (CEA and CA 27.29), and an echocardiography or radionuclide ventriculography.

Patients received four cycles of EC, with epirubicin (100 mg/m^2) and cyclophosphamide (600 mg/m^2) administered intravenously (IV) every 14 days. Granulocyte colony-stimulating factor was administered subcutaneously at 5 μg/kg daily from day (d) 3 to 10. Starting 2 weeks after the fourth cycle of $E_{100}C$, patients were given four cycles of docetaxel/capecitabine, with docetaxel (Taxotere®) (75 mg/m^2 IV, d1 of each cycle) and capecitabine (Xeloda®) at 1,000 mg/m^2 twice a day (b.i.d.) orally (PO), d1–14, administered every 21 days. During the four cycles of docetaxel/capecitabine, patients received levofloxacin at 500 mg daily PO, on d5–18 of each cycle, and pyridoxine 50 mg PO three times daily.

Patients receiving treatment preoperatively were required to undergo magnetic resonance imaging (MRI) and breast ultrasonography with axillary assessment prior to starting chemotherapy. These tests were repeated upon completion of treatment to evaluate clinical response. Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used for clinical response evaluation [17]. Surgery was performed 4–6 weeks after the last cycle. Pathological response was evaluated in the surgical specimens from the breast and axilla. A pCR required the eradication of viable invasive ductal carcinoma cells at both sites, with or without presence of ductal carcinoma in situ in the breast pathological specimen.

Dose modifications

In the case of incomplete hematologic recovery from the previous cycle (absolute neutrophil count <1,000/mm^3 and or platelets <75,000/mm^3), treatment was delayed until recovery. After each episode of grade 3–4 nonhematological toxicity treatment was withheld until resolution of

toxicity to ≤grade 1, and the doses of epirubicin and cyclophosphamide (if after EC) or of capecitabine (if after docetaxel/capecitabine) were reduced by 20%. The dose of docetaxel was not reduced for nonhematological toxicity. After each episode of neutropenic fever the doses of epirubicin and cyclophosphamide or docetaxel were reduced by 20%. The dose of capecitabine was not reduced for hematological toxicity.

Post-chemotherapy and post-surgical treatment

Since all patients in the study had axillary involvement or locally advanced tumors, the need for locoregional radiotherapy was assessed in all cases. Following completion of chemotherapy, premenopausal patients with hormone receptor-positive tumors received adjuvant hormonal therapy with tamoxifen for 5 years and a luteinizing hormone-releasing hormone analogue for 2 years; postmenopausal patients were treated with an aromatase inhibitor for 5 years. Patients were monitored every 6 months for 5 years upon treatment completion, and on a yearly basis thereafter.

Statistical design

Previous reports have established the separate feasibility of the two components of the treatment sequence, epirubicin/cyclophosphamide [18] and docetaxel/capecitabine [7], at the doses used in this study. In this trial, we intended to study the tolerability and activity of their sequential administration in the nonmetastatic setting. Toxicity was graded according to the Common Toxicity Criteria of the National Cancer Institute [19].

The trial followed a two-stage design. Twenty patients were accrued in the first stage of the study. If five or more patients experienced grade 3–4 toxicity, the lower limit of the 95% confidence interval of incidence of grade 3–4 toxicity would be greater than 5%. The dose of capecitabine (if nonhematological toxicities) and/or docetaxel (if hematological toxicities) would then be decreased by 20% for all patients.

If fewer than five patients among the first 20 experienced grade 3–4 toxicity then another 20 patients would be enrolled at the same dose. If the cumulative number of grade 3–4 toxic events among the 40 patients was 8 or more, the conclusion, with 95% probability, would be that the grade 3–4 toxicity rate exceeds 5%. If the cumulative number of grade 3–4 toxic events among the 40 patients was 15 or more, the conclusion would be that the grade 3–4 toxicity rate exceeds 20%, with 95% probability. This two-stage design has greater than 90% power to detect a 20% rate of grade 3–4 toxicity, with a type I error rate of 5% [20].

Event-free survival (EFS) was estimated from the first chemotherapy day until tumor progression, relapse, or death from any cause. Overall survival (OS) was estimated from the start of chemotherapy until death. The comparisons between the toxicity grades encountered in both trial stages employed the chi-square test.

Results

Patient enrollment

Fifty-five patients were enrolled and treated in this study between 1/2005 and 12/2006. Patient characteristics are listed in Table 1. Thirty-five patients with node-positive tumors after primary surgery received the treatment postoperatively. Twenty patients with locally advanced breast cancer who were deemed candidates for neoadjuvant chemotherapy were treated preoperatively.

Toxicity (Table 2)

Twenty patients treated in the first stage of the trial experienced skin toxicity, with 45% incidence of grade 3 hand–foot syndrome (HFS) and an additional 30% incidence of grade 2 HFS. One patient with grade 3 HFS discontinued treatment after her seventh cycle. This prompted a reduction in the dose of capecitabine from 1,000 to 800 mg/m^2 in the second stage of the trial, which enrolled 35 patients. Skin toxicity then became significantly less severe, with grade 3 and grade 2 HFS in 14 and 17% of the patients, respectively ($P = 0.009$ for grade 3, and $P = 0.009$ for combined grade 2–3 HFS).

None of the other observed toxicities necessitated a dose reduction, and their incidences did not differ significantly between the first and second stages of the trial. Grade 2 nail changes were seen in 30 and 23% of patients in the first and second stages, respectively ($P = 0.5$), and grade 1 nail changes were observed in 30 and 11% of patients, respectively. Stomatitis was mild throughout the study: the incidences were 10% for grade 2 and 5% for grade 1 in the first stage and 11% for grade 2 and 6% for grade 1 in the second stage. No patients in this study experienced peripheral neuropathy or a drop in the left ventricle ejection fraction. Five patients experienced neutropenic fever with grade 3 neutropenia after EC and three after docetaxel/capecitabine. The incidences of neutropenic fever in the first and second stages were 20 and 14%, respectively ($P = 0.6$). No grade 3–4 anemia or thrombocytopenia was observed. No grade 4–5 toxicities of any sort were seen throughout the trial.

None of the surgeries had to be delayed for patients treated preoperatively. There were no post-surgical complications in those cases.

Table 1 Patient Demographics ($N = 55$)

Age, median (range)	49 (27–73) years
Menopausal status	
Peri/Premenopausal	25 (45%)
Postmenopausal	30 (55%)
Histology	
Ductal	48 (87%)
Lobular	7 (13%)
Stage	
IIA	22 (40%)
IIB	9 (16%)
IIIA	19 (34%)
IIIB	3 (5%)
IIIC	2 (4%)
Tumor size, median (range)	2.5 (1–13) cm
Nodal status	
No. + nodes: median (range)	2 (1–13)
Nodal ratio: median (range)	0.3 (0.1–0.9)
Hormone receptors	
ER+ PR+	38 (69%)
ER+ PR−	4 (7%)
ER− PR+	2 (4%)
ER− PR−	11 (20%)
HER2 overexpression	0 (0%)
P53	
Negative	41 (73%)
Positive	12 (22%)
Undetermined	2 (4%)
Tumor grade	
1–2	18 (33%)
3	27 (49%)
Undetermined	10 (18%)
Ki67, % + cells: median (range)	15% (2–98%)
Initial treatment	
Chemotherapy	20 (36%)
Surgery	
BCS	24 (44%)
MRM	11 (20%)

Nodal ratio: no. positive nodes/no. dissected nodes

ER estrogen receptors, *PR* progesterone receptors, *BCS* breast-conserving surgery, *MRM* modified radical mastectomy

Tumor responses

All 20 patients treated preoperatively responded clinically as determined by MRI, ten of them with a CR. Fifteen patients underwent breast-conserving surgery and five patients had a modified radical mastectomy. Five patients (2 with stage IIIA and 3 with stage IIB tumors) experienced a pCR (25%, 95% confidence interval, 6–44%). Three additional patients had pT_0N_1 tumors in their surgical specimens.

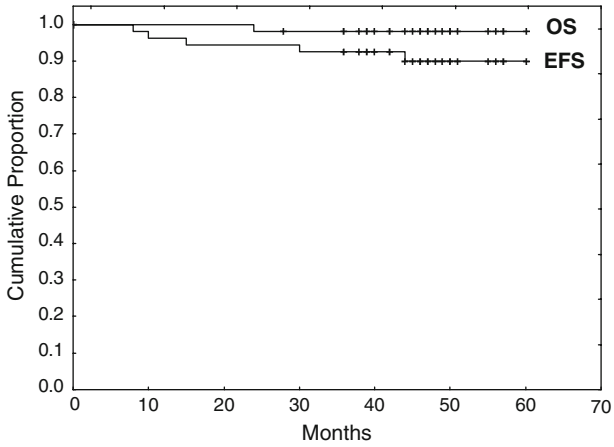

Fig. 1 Event-free survival (EFS) and overall survival (OS) curves of the study population

Post-chemotherapy treatment

Following completion of chemotherapy, 43 patients with hormone receptor-positive tumors were prescribed hormone treatment for 5 years. Locoregional radiotherapy was administered to 54 (98%) patients without unexpected side effects.

Outcome

At a median follow-up of 48 (range 28–60) months, five patients have had disease relapse, and one of them has died from progressive disease. The EFS and OS rates are 90.9 and 98.2%, respectively (Fig. 1).

The five patients whose tumor relapsed did not differ significantly from the other 50 patients in age ($P = 0.2$) or histological grade ($P = 0.9$). However, their tumors seemed to be larger (median 5.5 vs. 2.4 cm, $P = 0.1$), presented with more involved axillary nodes (median 6 vs. 2, $P = 0.00001$) and a higher axillary nodal ratio, defined as the quotient between the no. positive nodes and the no. dissected nodes (0.55 vs. 0.105, $P = 0.00001$), and showed a higher proliferative fraction (70 vs. 15% Ki67-positive cells, $P = 0.01$). Two of the five relapsing patients were treated neoadjuvantly, with a clinical CR and a partial response, respectively. The pathological stages in their surgical specimens were pT_1N_0 and pT_2N_2, respectively.

Discussion

The sequential combination of dose-dense EC followed by docetaxel/capecitabine in patients with node-positive or locally advanced tumors was well tolerated and showed very encouraging activity in this feasibility study. This new

Table 2 Grade 2–3 toxicities

	HFS		Nails		Mucositis		Neutropenic fever
	G2 (%)	G3 (%)	G2 (%)	G3 (%)	G2 (%)	G3 (%)	G3 (%)
1st stage ($N = 20$)	30	45	30	0	10	0	20
2nd stage ($N = 35$)	17	14	23	0	11	0	14
P value		0.009	0.5				0.6

sequential schema incorporates capecitabine, an effective agent in the metastatic setting, into the adjuvant or neoadjuvant treatment of breast cancer.

We elected to add capecitabine to a sequential framework of anthracyclines followed by docetaxel, because emerging data suggest that sequential treatment with these agents might be superior to their concurrent administration. Francis et al. compared both sequential and concurrent doxorubicin and docetaxel to a control arm of doxorubicin with or without cyclophosphamide, followed in all cases by cyclophosphamide/methotrexate/5-FU, and reported improved EFS in the sequential, but not the concurrent, experimental arm compared to control treatment [21]. Results of other randomized neoadjuvant trials are in keeping with these observations. Sequential doxorubicin–docetaxel resulted in higher response and pCR rates than doxorubicin alone in several studies [22–24]. In contrast, concurrent doxorubicin/docetaxel was not shown to be more active than doxorubicin/cyclophosphamide [25]. Finally, the use of a sequential arm of doxorubicin/cyclophosphamide followed by docetaxel resulted in higher response and pCR rates than a dose-dense regimen of concurrent doxorubicin/docetaxel [26].

The combination of docetaxel and capecitabine is attractive because of their different mechanisms of action and largely nonoverlapping side effects, namely, myelotoxicity and cutaneous/mucosal toxicity, respectively. In metastatic disease, docetaxel/capecitabine achieved superior RR, EFS and OS compared to docetaxel alone [7]. The synergy of the combination may be due to docetaxel-induced tumor upregulation of TP [8, 9], the enzyme responsible for the intracellular activation of capecitabine from 5′-FUDR to 5-FU. Preclinical observations have shown that transfecting cells with TP sensitizes them to 5′-FUDR[27–29] and that this compound is more active in TP-overexpressing tumor xenografts [30]. Furthermore, TP expression in tumor cells is a favorable predictive factor after treatment with 5′-FUDR in patients with breast cancer [10–12, 31, 32]. In a recent study, TP expression in metastatic tumor samples correlated directly with time to progression after treatment with docetaxel/capecitabine [13]. Further supporting the hypothesis of docetaxel-induced tumor sensitization to capecitabine, concurrent treatment of xenografts with docetaxel and capecitabine resulted in synergistic activity, whereas the combination of docetaxel with either 5-FU or uracil plus tegafur, neither of which require activation by TP, showed only additive activity [13].

The therapeutic schema tested in this trial pursues additional upregulation of TP by EC administered prior to docetaxel/capecitabine. Toi et al. [14] have described increased expression of TP in breast cancer specimens after preoperative chemotherapy with AC or EC but not after using 5-FU-containing regimens (i.e., FAC or FEC). It is possible that 5-FU selectively kills or suppresses TP-overexpressing cells or that, at high concentrations, 5-FU, a pyrimidine substrate, downregulates the expression of TP. Additional considerations about toxicity prompted us to use EC instead of FEC for the initial dose-dense part of the therapeutic sequence. In one adjuvant study, biweekly FEC was associated with excessive pericardial, pleural and pulmonary toxicity [33], whereas dose-dense EC can be administered without difficulty [34]. Thus, EC was a better fit for our strategy of administering dose-dense TP-upregulating chemotherapy followed by TP-dependent chemotherapy.

In the original phase I evaluation of docetaxel/capecitabine, the dose of capecitabine considered to be feasible was identified as 1,250 mg/m^2 b.i.d. for 14 days, combined with 75 mg/m^2 of docetaxel, every 3 weeks [35]. When compared to docetaxel in MBC, these doses of docetaxel/capecitabine were associated with a manageable 24% incidence of grade 3 HFS [7]. Subsequent reports of dose reductions of capecitabine to 950 mg/m^2 suggested that the toxicity of the regimen could be ameliorated without compromising its efficacy [36]. In contrast to the latter observations, our starting capecitabine dose of 1,000 mg/m^2 caused excessive HFS. A subsequent protocol-mandated dose reduction to 800 mg/m^2 improved the tolerability of docetaxel/capecitabine. The paradoxical observation of greater toxic effects from capecitabine in our nonmetastatic patients than in prior reports from the metastatic setting may be explained by the upregulation of TP by EC. Since TP is preferentially expressed in tumor cells [37, 38], the combined effect of TP upregulation and subsequent dose reduction of capecitabine should, at least in theory, improve its therapeutic index.

There is growing interest in the use of capecitabine in the adjuvant setting. Joensuu and colleagues [39] recently reported an interim safety analysis in a subset of 600 patients enrolled in a randomized trial of docetaxel/

Table 3 Trials testing docetaxel/capecitabine as neoadjuvant treatment

Study	*N*	Schema	Docetaxel/capecitabine schedule	T stage				HR		HER2		pCR rate[a]
				T_1	T_2	T_3	T_4	Negative	Positive	Negative	Positive	
GeparQuattro	1,510	EC → Doc EC → Doc/Cap EC → Doc → Cap (+Trastuzumab if HER2+)	Doc: 75 mg/m^2 IV, d1 Cap: 900 mg/m^2 PO BID, d1–14, Every 3 weeks	Not specified				Not specified		70%	30%	21% in all three arms
Lee	103	Doc/Cap	Doc: 75 mg/m^2 IV, d1 Cap: 1,000 mg/m^2 PO BID, d1-14 Every 3 weeks	79%		21%		38%	62%	46% 22% unknown	32%	15%
Natoli	41	EC → Doc/Cap	Doc: 36 mg/m^2 IV, d1, 8 and 15 Cap: 1,250 mg/m^2 PO BID, d5–18 Every 4 weeks	0%	70%	30%	0%	41%	59%	61%	39%	17%
Layman	26	Doc/Cap → AC	Doc: 36 mg/m^2 IV, d1, 8 and 15 Cap: 1,000 mg/m^2 PO BID, d5–21 Every 4 weeks	8%	69%	23%	0%	58%	42%	77%	23%	27%
Present	20	EC → Doc/Cap	Doc: 75 mg/m^2 IV, d1 Cap: 800-1,000 mg/m^2 PO BID, d1-14 every 3 weeks	5%	35%	45%	15%	20%	80%	100%	0%	25%

[a] pCR assessed in breast and axilla

HR hormone receptors, *pCR* pathologic complete response, *IV* intravenously, *PO* orally, *BID* twice daily, *EC* epirubicin/cyclophosphamide, *AC* doxorubicin/cyclophosphamide, *Doc* docetaxel, *Cap* capecitabine

capecitabine at a similar dose and schedule but in the inverse therapeutic sequence to ours. These authors compared in 1,500 patients with node-negative and node-positive disease the use of three cycles of docetaxel (60 mg/m^2)/capecitabine (900 mg/m^2 b.i.d., d1–15) followed by three cycles of cyclophosphamide (600 mg/m^2)/epirubicin (75 mg/m^2)/capecitabine (900 mg/m^2 b.i.d., d1–15), to a control arm that received three cycles of docetaxel alone (75 mg/m^2) followed by three cycles of FEC, all cycles administered every 3 weeks. The toxicity profile (9.6% incidence of grade 3–4 HFS) of docetaxel/capecitabine seen in this patient subset was similar to that we observed in the second stage of our study.

The preoperative activity of our regimen, evidenced by a 25% pCR rate in the small subset of patients with LABC, is encouraging, particularly in view of the fact that our patients had tumor phenotypes (HER2-negative and largely hormone receptor-positive) associated with lower pCR rates after preoperative chemotherapy [40–42]. Our use of triweekly docetaxel is supported by reports of single-agent docetaxel having greater activity when given every 3 weeks as compared to weekly, in both the adjuvant [43] and metastatic settings [44]. Lee and collaborators compared neoadjuvant docetaxel/capecitabine (at the same doses as in the first stage of our trial) with AC, both given every 3 weeks [45]. This trial enrolled 209 patients, mostly with stage II tumors. The pCR rate in the breast and axilla was higher after docetaxel/capecitabine than after AC (15 vs. 7%). Other authors have tested preoperatively a variant schedule in which docetaxel/capecitabine was administered monthly, with weekly doses of docetaxel at 36 mg/m^2 (days 1, 8 and 15) and capecitabine at 500–625 mg/m^2 bid for 14–17 days from day 5 of each cycle. Layman et al. [46] treated 26 patients, most of whom had T_1–T_2 and hormone receptor-negative tumors, with the variant docetaxel/capecitabine schedule. The pCR rate in their trial was only 7.6% after four cycles of docetaxel/capecitabine, but it increased to 26.9% after an additional four courses of dose-dense AC. Natoli et al. [47] employed a similar sequence to ours, with four cycles of dose-dense EC (90/600 mg/m^2) followed by four cycles of variant docetaxel/capecitabine in 44 patients, most of them with T_2 tumors. The pCR rate in their trial was 17% (8% among 24 patients with HER2-negative tumors).

The randomized GeparQuattro trial compared the preoperative use of four cycles EC (90/600 mg/m^2) every 3 weeks followed by either four cycles of docetaxel alone at 100 mg/m^2, four cycles of concomitant docetaxel/capecitabine (60/900 mg/m^2 every 12 h × 15 days) every 3 weeks, or the sequential use of four cycles of docetaxel (75 mg/m^2) followed by four cycles of capecitabine (900 mg/m^2 every 12 h) [48, 49]. This study enrolled 1,510 patients with operable tumors. Trastuzumab was added to chemotherapy for the 30% of patients with HER2-positive tumors. The first interim analysis of toxicity showed a 27.6% incidence of grade 3–4 HFS in the concomitant docetaxel/capecitabine arm, which appears higher than that observed in the second phase of our study (14%), perhaps due to the use of a slightly higher dose of capecitabine. The first preliminary analysis of responses showed no differences between the three arms, with pCR rates of around 21% in all three. Important differences between this study and ours were the inclusion in GeparQuattro of patients with smaller tumors and with HER2-positive disease, the latter group treated with concurrent trastuzumab-chemotherapy. Both groups of patients typically achieve higher pCR rates than the population of patients with larger and HER2-negative tumors we targeted in our trial [40–42].

Although the subset of patients treated preoperatively in our study had bigger tumors and a higher prevalence of hormone receptor-positive and HER2-negative disease, the pCR rate appears to compare favorably with that achieved in those other neoadjuvant trials (Table 3). Therefore, it is conceivable that differences in total duration (4, 6, or 8 cycles) and schedule (anthracyclines followed by docetaxel/capecitabine or vice versa) of chemotherapy, or the use of triweekly versus weekly docetaxel may be relevant to the antitumor activity of docetaxel/capecitabine, as well as possible differences in activity between dose-dense and triweekly EC. While our preoperative results are limited by the small size of this subset of patients and our outcome observations need longer follow-up, we believe that this regimen, as tested in this trial, is highly promising and worthy of further testing.

In conclusion, sequential treatment with dose-dense EC followed by docetaxel/capecitabine, using a lower capecitabine dose than that approved for MBC, has an acceptable toxicity profile and encouraging activity when used as neoadjuvant or adjuvant treatment of breast cancer.

References

1. Citron ML, Berry DA, Cirrincione C et al (2003) Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:1431–1439
2. Henderson IC, Berry DA, Demetri GD et al (2003) Improved outcomes from adding sequential Paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 21:976–983
3. Mamounas EP, Bryant J, Lembersky BC et al (2005) Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol 23:3686–3696
4. Gianni L, Baselga J, Eiermann W et al (2005) Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by

cyclophosphamide, methotrexate, and fluorouracil and its effects on tumor response as preoperative therapy. Clin Cancer Res 11:8715–8721
5. Martín M, Pienkowski T, Mackey J et al (2005) Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 352:2302–2313
6. Roché H, Fumoleau P, Spielmann M et al (2004) Five years analysis of the PACS 01 trial: 6 cycles of FEC100 vs 3 cycles of FEC100 followed by 3 cycles of docetaxel (D) for the adjuvant treatment of node-positive breast cancer. Breast Cancer Res Treat 88(Suppl 1):S16
7. O'Shaughnessy J, Miles D, Vukelja S et al (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III results. J Clin Oncol 20:2812–2823
8. Sawada N, Ishikawa T, Fukase Y et al (1998) Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. Clin Cancer Res 4:1013–1019
9. Kurosumi M, Tabei T, Suemasu K et al (2000) Enhancement of immunohistochemical reactivity for thymidine phosphorylase in breast carcinoma cells after administration of docetaxel as a neoadjuvant chemotherapy in advanced breast cancer patients. Oncol Rep 7:945–948
10. Takahashi H, Maeda Y, Watanabe K et al (2000) Correlation between elevated intratumoral thymidine phosphorylase and prognosis of node-positive breast carcinoma undergoing adjuvant doxifluridine treatment. Int J Oncol 17:1205–1211
11. Yang Q, Barbareschi M, Mori I et al (2002) Prognostic value of thymidine phosphorylase expression in breast carcinoma. Int J Cancer 97:512–517
12. Tominaga T, Toi M, Ohashi Y et al (2002) Prognostic and predictive value of thymidine phosphorylase activity in early-stage breast cancer patients. Clin Breast Cancer 3:55–64
13. Puglisi F, Cardellino GG, Crivellari D et al (2008) Thymidine phosphorylase expression is associated with time to progression in patients receiving low-dose, docetaxel-modulated capecitabine for metastatic breast cancer. Ann Oncol 19:1541–1546
14. Toi M, Bando H, Horiguchi S et al (2004) Modulation of thymidine phosphorylase by neoadjuvant chemotherapy in primary breast cancer. Br J Cancer 90:2338–2343
15. Pegram M, Hsu S, Lewis G et al (1999) Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers. Oncogene 18:2241–2251
16. Pegram MD, Lopez A, Konecny G, Slamon DJ (2000) Trastuzumab and chemotherapeutics: drug interactions and synergies. Semin Oncol 27(6 Suppl 11):21–25
17. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
18. Piccart M, Di Leo A, Beauduin M et al (2001) Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. J Clin Oncol 19:3103–3110
19. http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf
20. Fleming TR (1982) One-sample multiple testing procedure for phase II clinical trials. Biometrics 38:143–151
21. Francis P, Crown JP, Di Leo A et al (2008) Adjuvant chemotherapy with sequential of concurrent and anthracycline and docetaxel: Breast International Group 02–98 randomized trial. J Natl Cancer Inst 100:121–133
22. Smith IC, Heys SD, Hutcheon AW et al (2002) Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol 20:1456–1466
23. Bear HD, Anderson S, Brown A et al (2003) The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 21:4165–4174
24. Bear HD, Anderson S, Smith RE et al (2006) Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 24:2019–2027
25. Evans TR, Yellowlees A, Foster E et al (2005) Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: an anglo-celtic cooperative oncology group study. J Clin Oncol 23:2988–2995
26. Von Minckwitz G, Raab G, Caputo A et al (2005) Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. J Clin Oncol 23:2676–2685
27. Patterson AV, Zhang H, Moghaddam A et al (1995) Increased sensitivity to the prodrug 5′-deoxy-5-fluorouridine and modulation of 5-fluoro-2′-deoxyuridine sensitivity in MCF-7 cells transfected with thymidine phosphorylase. Br J Cancer 72:669–675
28. Evrard A, Cuq P, Ciccolini J et al (1999) Increased cytotoxicity and bystander effect of 5-fluorouracil and 5-deoxy-5-fluorouridine in human colorectal cancer cells transfected with thymidine phosphorylase. Br J Cancer 80:1726–1733
29. Morita T, Matsuzaki A, Tokue A (2001) Enhancement of sensitivity to capecitabine in human renal carcinoma cells transfected with thymidine phosphorylase cDNA. Int J Cancer 92:451–456
30. Ishikawa T, Sekiguchi F, Fukase Y et al (1998) Positive correlation between the efficacy of capecitabine and doxifluridine and the ratio of thymidine phosphorylase to dihydropyrimidine dehydrogenase activities in tumors in human cancer xenografts. Cancer Res 58:685–690
31. Fox SB, Engels K, Comley M et al (1997) Relationship of elevated tumour thymidine phosphorylase in node-positive breast carcinomas to the effects of adjuvant CMF. Ann Oncol 8:271–275
32. Gasparini G, Toi M, Miceli R et al (1999) Clinical relevance of vascular endothelial growth factor and thymidine phosphorylase in patients with node-positive breast cancer treated with either adjuvant chemotherapy or hormone therapy. Cancer J Sci Am 5:101–111
33. Dang CT, D'Andrea GM, Moynahan ME et al (2004) Phase II study of feasibility of dose-dense FEC followed by alternating weekly taxanes in high-risk, four or more node-positive breast cancer. Clin Cancer Res 10:5754–5761
34. Therasse P, Mauriac L, Welnicka-Jaskiewicz M et al (2003) Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide + filgrastim as neoadjuvant treatment in locally advanced breast cancer: an EORTC-NCIC-SAKK multicenter study. J Clin Oncol 21:843–850
35. Pronk LC, Vasey P, Sparreboom A et al (2000) A phase I and pharmacokinetic study of the combination of capecitabine and docetaxel in patients with advanced solid tumours. Br J Cancer 83:22–29
36. Leonard R, O'Shaughnessy J, Vukelja S et al (2006) Detailed analysis of a randomized phase III trial: can the tolerability of capecitabine plus docetaxel be improved without compromising its survival advantage? Ann Oncol 17:1379–1385
37. Miwa M, Ura M, Nishida M et al (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
38. Schuller J, Cassidy J, Dumont E et al (2000) Preferential activation of capecitabine in tumor following oral administration

to colorectal cancer patients. Cancer Chemother Pharmacol 45:291–297
39. Joensuu H, Hemminki A, Huovinen M et al (2007) The FinXX trial: safety results in 600 patients (pts) randomized to either docetaxel (T) followed by cyclophosphamide (C)+ epirubicin (E)+ 5-FU (F) (CEF) or T+ capecitabine (X) followed by CEX as adjuvant therapy for early breast cancer (BC). J Clin Oncol 25:18S abstract 1103
40. André F, Mazouni C, Liedtke C et al (2008) HER2 expression and efficacy of preoperative paclitaxel/FAC chemotherapy in breast cancer. Breast Cancer Res Treat 108:183–190
41. Colleoni M, Viale G, Zahrieh D et al (2004) Chemotherapy is more effective in patients with breast cancer not expressing steroid hormone receptors: a study of preoperative treatment. Clin Cancer Res 10:6622–6628
42. Gianni L, Zambetti M, Clark K et al (2005) Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer. J Clin Oncol 23:7265–7277
43. Sparano JA, Wang M, Martino S et al (2008) Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 358:1663–1671
44. Rivera E, Mejia JA, Arun BK et al (2008) Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. Cancer 112:1455–1461
45. Lee KS, Ro J, Nam B-H et al (2008) A randomized phase-III trial of docetaxel/capecitabine versus doxorubicin/cyclophosphamide as primary chemotherapy for patients with stage II/III breast cancer. Breast Cancer Res Treat 109:481–489
46. Layman RM, Thomas DG, Griffith KA et al (2007) Neoadjuvant docetaxel and capecitabine and the use of thymidine phosphorylase as a predictive biomarker in breast cancer. Clin Cancer Res 13:4092–4197
47. Natoli C, Cianchetti E, Tinari N et al (2007) A phase II study of dose-dense epirubicin plus cyclophosphamide followed by docetaxel plus capecitabine and pegfilgrastim support as preoperative therapy for patients with stage II, IIIA breast cancer. Ann Oncol 18:1015–1020
48. Untch M, Rezai M, Loibl S et al (2007) Evaluating the efficacy and safety of trastuzumab given concomitantly to epirubicin/cyclophosphamide → docetaxel ± capecitabine as neoadjuvant treatment of HER2 overexpressing primary breast cancer First analysis of the GBG/AGO intergroup study "GeparQuattro". Breast Cancer Res Treat 106(Suppl 1):S224
49. von Minckwitz G, Rezai M, Loibl S et al (2008) Capecitabine given concomitantly or in sequence with EC → docetaxel as neoadjuvant treatment for early breast cancer: GeparQuattro–a GBG/ABO intergroup study. Eur J Cancer Suppl 6:108