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A phase II study of epirubicin, cisplatin and capecitabine as neoadjuvant chemotherapy in locally advanced or inflammatory breast cancer ☆

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ABSTRACT

Aim: To assess the efficacy and safety of epirubicin, capecitabine and cisplatin (EXC) combination therapy in locally advanced breast cancer (LABC) and investigate the predictive value of selected biomarkers.

Methods: Newly diagnosed LABC patients received four 3-weekly cycles of neoadjuvant EXC (epirubicin 60 mg/m^2 day 1; capecitabine 1000 mg/m^2 bid, days 1–14; cisplatin 60 mg/m^{2}day 1) and two cycles of post-operative EXC.

Results: Eight (17%) of 48 patients had inflammatory breast cancer. Overall response rate was 74% (95% CI: 59–86%), including complete responses in 13% (95% CI: 5–26%). Nine (22%; 95% CI: 11–38%) of 41 patients undergoing surgery achieved pathologic complete response (pCR), giving a pCR rate of 19% (95% CI: 9–33%) in the intent-to-treat population. Haematological toxicity was manageable. The most problematic toxicities were chemotherapy-induced nausea/vomiting and hypercoagulative disorders. None of the biomarkers investigated, including HER2, predicted response.

Conclusion: EXC showed high efficacy in LABC, with high clinical response and pCR rate. Nausea and vomiting were unexpectedly frequent, and more aggressive prophylaxis and management of these side effects is recommended in future studies of this combination.

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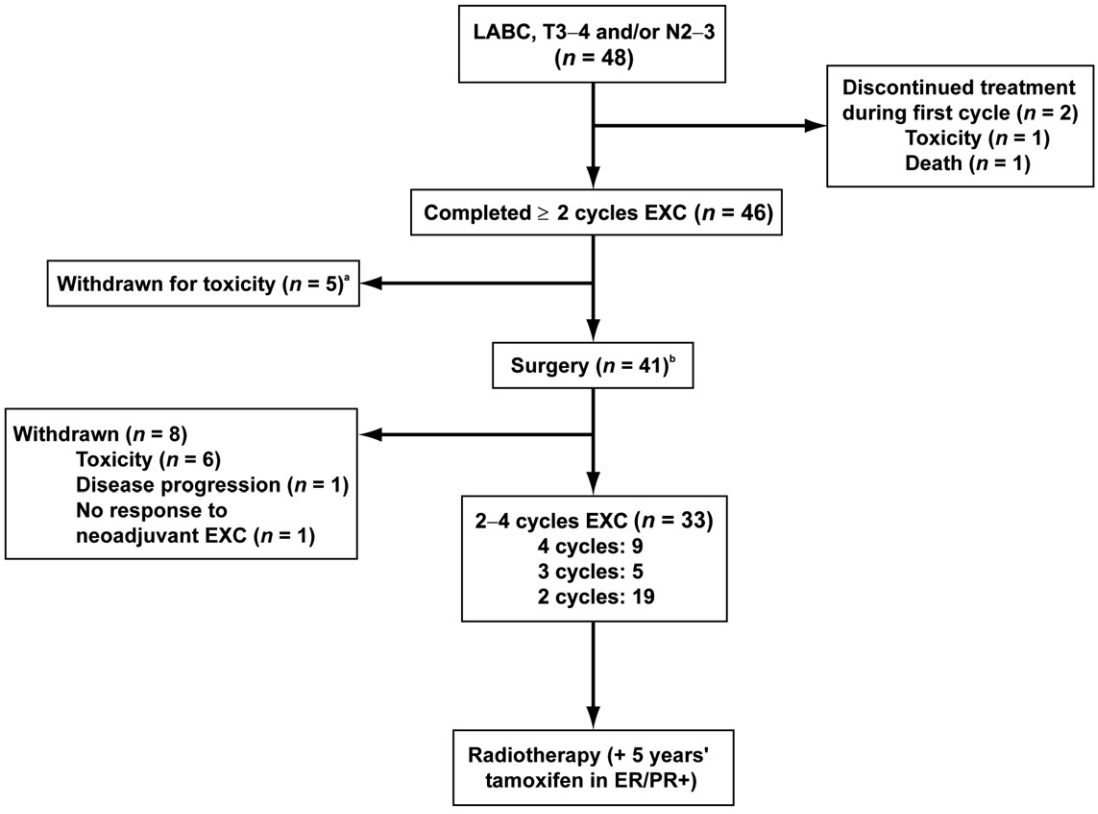
1. Introduction

Despite wide use of screening mammography, locally advanced breast cancer (LABC) remains a major clinical problem. Neoadjuvant chemotherapy is typically administered with the aim of downstaging tumours and increasing the rate of breast-conserving surgery.[1] Neoadjuvant therapy may be selected instead of or as well as adjuvant therapy as it provides earlier exposure to systemic chemotherapy and may improve surgical options. Treatment typically involves anthracycline-containing neoadjuvant chemotherapy, but prognosis is poor. In a Swedish study,[2] 5-year disease-free survival (DFS) rate was only 36% despite multimodality treatment with standard-dose anthracycline-based chemotherapy. Conventional anthracycline dose intensification did not improve response rate (RR) or overall survival (OS) compared with standard-dose anthracyclines.[3,4]

In an attempt to improve outcomes, several newer agents, including docetaxel, paclitaxel, capecitabine and platinum salts, are being assessed as primary chemotherapy for breast cancer. Although the addition of docetaxel to neoadjuvant anthracycline therapy failed to improve efficacy,[5] sequential administration of neoadjuvant anthracycline-based chemotherapy followed by docetaxel improved RR and pathologic complete response (pCR) rate compared with anthracycline-based therapy alone.[6,7] In the Aberdeen trial, sequential docetaxel improved OS and DFS,[8] although in the much larger NSABP-27 trial, the 2-fold increase in pCR rate did not translate into an OS gain.[6]

Capecitabine, an oral fluoropyrimidine, has demonstrated high activity and good tolerability both as monotherapy and as a component of several combination regimens.[9–11] Capecitabine plus docetaxel is now a standard of care in anthracycline-pretreated metastatic breast cancer, and the combination is significantly more active than sequential docetaxel followed by capecitabine as first-line therapy.[11,12] Consequently, capecitabine-based regimens are being evaluated earlier in the disease course, including the adjuvant and neoadjuvant settings.

This study aimed to evaluate the efficacy and safety of epirubicin, capecitabine and cisplatin (EXC) combination therapy in LABC. Doses were selected based on early findings from the TOPIC trial evaluating continuous infusion 5-fluorouracil (5-FU), epirubicin and cisplatin[13] and a Scottish phase I study of EXC in advanced oesophago-gastric carcinoma.[14] We also investigated the predictive value of HER2 and topoisomerase



[a]Chemotherapy modified in 4 patients, radiotherapy given in 1 patient.

[b]Among 41 patients undergoing surgery, 38 received 4 cycles of neoadjuvant EXC, 1 received 3 cycles and 2 received 2 cycles.

Fig. 1 – Study design. ER, oestrogen receptor; EXC, epirubicin, capecitabine, cisplatin; LABC, locally advanced breast cancer; PR, progesterone receptor.

IIα (TOP2A) status, and the enzymes thymidine phosphorylase (TP), thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD). HER2 and TOP2A were evaluated because amplification of these genes may be associated with enhanced response to anthracycline-containing chemotherapy.[15] TP, TS and DPD were investigated because they are involved in the three-step activation of capecitabine preferentially in tumour tissue[16] and may predict response to capecitabine.[17]

2. Patients and methods

2.1. Study design and treatment

This open-label, phase II study included women with newly diagnosed LABC, defined as tumours >50 mm (T3) and/or T4 and/or N2–3 status considered inoperable at the time of diagnosis. Despite downstaging by neoadjuvant chemotherapy, modified radical mastectomy was recommended in all patients. The study was performed at 10 Swedish Oncology Departments and was approved by local ethical committees and regulatory authorities. Eligible patients were ⩾18 years old. Patients >70 years old were eligible only on the basis of an individual risk:benefit assessment by the investigator. All patients provided written informed consent. Exclusion criteria included haemoglobin <100 g/l, neutrophil count $<1.5\times10^9$/l, platelet count $<100\times10^9$/l, renal clearance <60 ml/min (tested only if serum creatinine >100 μmol/l), bilirubin >1.25 × upper normal limit (UNL), alanine aminotransferase and/or aspartate aminotransferase >2 × UNL, or alkaline phosphatase >2 × UNL. All patients underwent chest X-ray, liver function tests and investigations, and bone scintigraphy to exclude a diagnosis of metastatic disease. Patients with abnormal bone scintigrams were eligible if further investigations failed to confirm metastatic disease.

Patients received four 3-weekly cycles of EXC (epirubicin 60 mg/m^2 i.v. bolus injection or 15-min i.v. infusion on day 1; cisplatin 60 mg/m^2 60-min i.v. infusion with adequate i.v. hydration on day 1; oral capecitabine 1000 mg/m^2 twice daily, days 1–14). An anti-emetic schedule including a selective $5HT_3$ antagonist and steroids was recommended. Patients then underwent modified radical mastectomy. Originally, patients were to receive four cycles of post-operative EXC starting within 2–4 weeks after surgery. Following protocol amendment in April 2001, the number of adjuvant cycles was reduced to two (total six cycles) to improve tolerability. After completing chemotherapy, post-mastectomy radiotherapy was administered according to local guidelines. Patients with hormone receptor-positive tumours received tamoxifen 20 mg/day for 5 years. Patients were assessed at 3-monthly intervals for the first 2 years and then at 6-monthly intervals for 3 years. The study design is outlined in Fig. 1.

The study was conducted according to good clinical practice (GCP) guidelines.

2.2. Dose modifications

For grade 1 toxicities no dose adjustments were made. At the first appearance of grade 2 toxicity, treatment was interrupted or delayed until resolution to grades 0–1, then restarted without dose reduction. At the second and third grade 2 occurrence of the same toxicity, dose was reduced to 75% and 50% of the original dose, respectively, after resolution to grades 0–1. For grade 3 toxicity, treatment was interrupted or delayed until resolution to grades 0–1, then restarted at 75% of the original dose. If a grade 3 toxicity recurred, the dose was reduced to 50%. Treatment was discontinued at the third grade 3 occurrence. No dose modification was required for anaemia. If the toxicity had not resolved when the start of the next cycle was due, all three drugs were delayed for 1 week until resolution of the toxicity or recovery of haematological parameters (maximum of three 1-week delays). Investigators could choose to reduce the dose of only one or two of the drugs according to the toxicity observed. Epirubicin was reduced to 75% of the original dose for subsequent cycles if at day 21 or 22 neutrophils were $0.5–0.9\times10^9$/l or platelets were $50–99\times10^9$/l, and to 50% if neutrophils were $<0.5\times10^9$/l or platelets were $<50\times10^9$/l. Treatment was withheld if neutrophils were $<1.5\times10^9$/l or platelets were $<100\times10^9$/l at the start of a new cycle. Cisplatin and epirubicin treatment was not modified (dose or schedule) in the event of hand-foot syndrome, diarrhoea or mucositis. If grade 2 diarrhoea did not resolve within 2 days of interrupting capecitabine treatment, capecitabine was restarted at resolution at a lower dose. In the event of ototoxicity, peripheral neuropathy or nephrotoxicity, capecitabine and epirubicin treatment was not modified. Serum creatinine clearance was tested if serum creatinine was >100 μmol/l or increased by 20% above baseline. If creatinine clearance was <60 ml/min, cisplatin was discontinued. Capecitabine dose modification or discontinuation according to creatinine clearance was not stipulated in the protocol.

2.3. Assessment of response and toxicity

Clinical response was evaluated after cycles 2 and 4 according to World Health Organization (WHO) criteria. Responses were not confirmed after 4 weeks because surgery was performed after the fourth cycle. Clinical response rate was defined as the proportion of patients achieving clinical complete or partial response as best clinical response between first dose of study treatment and progressive disease or end of study. pCR was defined as neither invasive nor *in situ* cancer in the breast and axillary lymph nodes. Toxicity was assessed according to National Cancer Institute of Canada Common Toxicity Criteria (CTC 2.0) after each cycle of EXC.

2.4. Analysis of biomarkers

Total RNA was isolated from snap-frozen needle biopsies using the RNeasy Mini Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. RNA and first flow-through of the RNA isolation step were stored at −70 °C until use. Reverse transcription and quantitative polymerase chain reaction (PCR), as well as TP, TS, and DPD mRNA quantification were performed with the LightCycler® kits, reagents and instrument from Roche Diagnostics GmbH (Mannheim, Germany), according to the manufacturer's instructions.

For evaluation of HER2 status, genomic DNA containing first flow-through of the mRNA extraction procedure was

purified using the QIAamp Mini Kit protocol (Qiagen, Valencia, CA, USA). DNA quality and quantity were assessed in the NanoDrop spectrophotometer (Nano Drop Technologies, Wilmington, DE, USA) and DNA was subjected to quantitative real-time PCR. HER2 status was determined using the LightCycler® HER2/neu DNA Quantification Kit. A ratio of $\geqslant$2.0 is considered to be positive for HER2 amplification.

HER2 status was also analysed by fluorescence *in situ* hybridisation (FISH) using the PathVysion HER2 DNA Probe Kit (Vysis Inc., Downers Grove, IL, USA), according to the manufacturer's instructions, and by using a Leica DMLB microscope (Wetzlar, Germany). A ratio of >2.0 was considered amplified. H. Nordgren performed the scoring.

2.5. Statistics

Sample size calculation was based on a Simon two-stage design.[18] The primary efficacy parameter was clinical RR (complete or partial response). A regimen yielding <50% RR would be of little interest, whereas RR $\geqslant$ 70% would be promising. Although other regimens have produced clinical RR higher than 70%, it is more important to avoid rejecting an efficacious therapy than accepting an inefficacious regimen in phase II studies, as efficacy will be further tested in phase III trials. With a power of 80% and an α-level of 5% (one-sided test), 43 evaluable patients were required. Assuming that only 90% would be evaluable, target accrual was 47 patients. The null-hypothesis could be rejected and the study continued if at least nine of the first 15 evaluable patients achieved objective responses. Histopathological response rate, time to relapse, survival, toxicity and predictive value of selected biomarkers were secondary endpoints. DFS was calculated from the date treatment started; OS was calculated from the date of breast cancer diagnosis, as specified in the protocol. The Kaplan–Meier method was used to estimate time to relapse and survival. Differences in survival between groups were tested using log-rank statistics. Biomarker data were evaluated by ANOVA analysis with post hoc testing according to Tukey–Kramer (α = 0.05) for continuous variables and χ_2 testing in cross tabulation for dichotomous data. Spearman correlation analysis was performed between different HER2 measurements.

3. Results

A total of 48 women with LABC were included in the study between January 2000 and February 2001. Median age was 48 years (range 33–69). Eight patients (17%) had inflammatory breast carcinoma (IBC) and 40 (83%) had non-inflammatory LABC. Baseline characteristics are summarised in Table 1.

Table 1 – Patient and tumour characteristics at diagnosis (*n* = 48)

	No. of patients	Patients (%)
Menopausal status		
Pre-menopausal	28	58
Post-menopausal	17	35
Uncertain	3	6
Tumour stage[a]		
IIB	15	31
IIIA	24	50
IIIB	8	17
IIIC	1	2
Histological tumour type		
Ductal	37	77
Lobular	8	17
Other	3	6
Oestrogen receptor		
Positive	29	60
Negative	16	33
Unknown	3	6
Progesterone receptor		
Positive	22	46
Negative	20	42
Unknown	6	13

a In one woman with bilateral breast cancer, the left-sided tumour (cT3N0) was included in the primary efficacy analysis, but the right-sided tumour (cT2N0) was omitted because it did not fulfil the entry criteria.

3.1. Treatment administered

All 48 patients completed at least one cycle and are included in the OS and safety analyses. In total, 263 cycles of EXC were administered: 175 neoadjuvant cycles (median 4, range 1–6) and 88 adjuvant cycles (median 2, range 2–4). Only one patient received more than the planned four neoadjuvant cycles: in this patient, the investigator decided to give two additional cycles instead of surgery following a venous thrombosis after the fourth cycle. Clinical response data are available for 46 patients (96%) who received at least two cycles of treatment at > 50% of the recommended doses and are therefore included in the protocol-defined population for clinical response assessment. Only 38 of 48 patients (79%) received the planned four cycles of neoadjuvant EXC (Fig. 1). An additional three patients underwent surgery, two patients after receiving only two cycles of EXC due to toxicity and one patient after three cycles due to investigator decision. The mean delivered versus planned dose of cisplatin was maintained at 99% (SD 5%) for all four neoadjuvant cycles, whereas mean epirubicin and capecitabine doses gradually decreased to 90% (SD 15%) and 91% (SD 22%), respectively, by the fourth cycle. After surgery, nine women received four cycles of EXC (prior to protocol amendment), five received three cycles, 19 received two cycles, and eight received no adjuvant EXC. The reasons for not administering post-operative EXC were treatment-related toxicity in six patients (primarily fatigue, gastrointestinal toxicities and hand-foot syndrome), disease progression in one and no response to neoadjuvant treatment in one.

3.2. Anti-tumour activity and survival

The RR among 46 patients completing at least two cycles of therapy was 74% (95% CI: 59–86%), including complete responses in 13% (95% CI: 5–26%). Forty-one EXC-treated patients underwent breast surgery. Five patients were withdrawn due to toxicity. Of these, four received other chemotherapy regimens and one received radiotherapy. Consequently, they were not evaluable for histopathological response. Nine patients achieved a pCR, giving a pCR rate in

the intent-to-treat population of 19% (95% CI: 9–33%), and 22% (95% CI: 11–38%) in EXC-treated patients who underwent surgery. In two patients without pCR, residual cancer cells were found only in lymph nodes.

Median follow-up is 35 months (range 0–44). No patients were lost to follow-up. During the follow-up period nine patients experienced disease recurrence and seven died. Although the study was not designed to formally compare efficacy according to disease type, OS and DFS were significantly shorter in patients with IBC versus non-inflammatory disease ($P \leqslant 0.00002$). Disease relapsed in only one of nine patients achieving pCR ($P = 0.39$).

3.3. *Safety*

Apart from alopecia, the most common treatment-related adverse events were nausea, fatigue, vomiting, hand-foot syndrome and stomatitis (Fig. 2). Haematological toxicity was generally manageable: grade 3/4 leucopenia occurred in 31% of patients and only three episodes of febrile neutropenia were observed. Despite dose reductions (of capecitabine and epirubicin, but rarely cisplatin) and treatment interruptions, grade 3/4 adverse events were frequent throughout the treatment period. There were two treatment-related deaths. A 68-year-old patient died 43 days after starting the first neoadjuvant cycle from septic shock caused by intestinal necrosis and grade 4 neutropenia after the first cycle. The second death was a 53-year-old patient who had a venous sinus thrombosis after her second post-operative cycle: the fall during anti-coagulant therapy caused head injury leading to lethal intracerebral haemorrhage. Four additional patients experienced possible hypercoagulative disorders: a second patient was diagnosed with a venous sinus thrombosis after her fourth post-operative cycle, which was not lethal but resulted in neurological sequelae; two patients had deep vein thrombosis (one after cycle 4 and one after her second post-operative cycle); and one had splenic infarction after cycle 2.

3.4. *Predictive markers*

Tumour specimens were available from 43 patients. The technical success rate for the PCR analysis of TS, TP and DPD was 84% (36/43). TS, TP and DPD concentrations and TP:DPD ratios were not significantly associated with response.

Due to a low (28/43, 65%) success rate with the initial HER2 and TOP2A FISH assessment due to suboptimal tumour sampling and shortage of evaluable tumour tissue, these data are not presented. We re-evaluated all 43 samples by quantitative real-time PCR for HER2 as described above. This produced a 91% (39/43) sample success rate and HER2 amplification rate

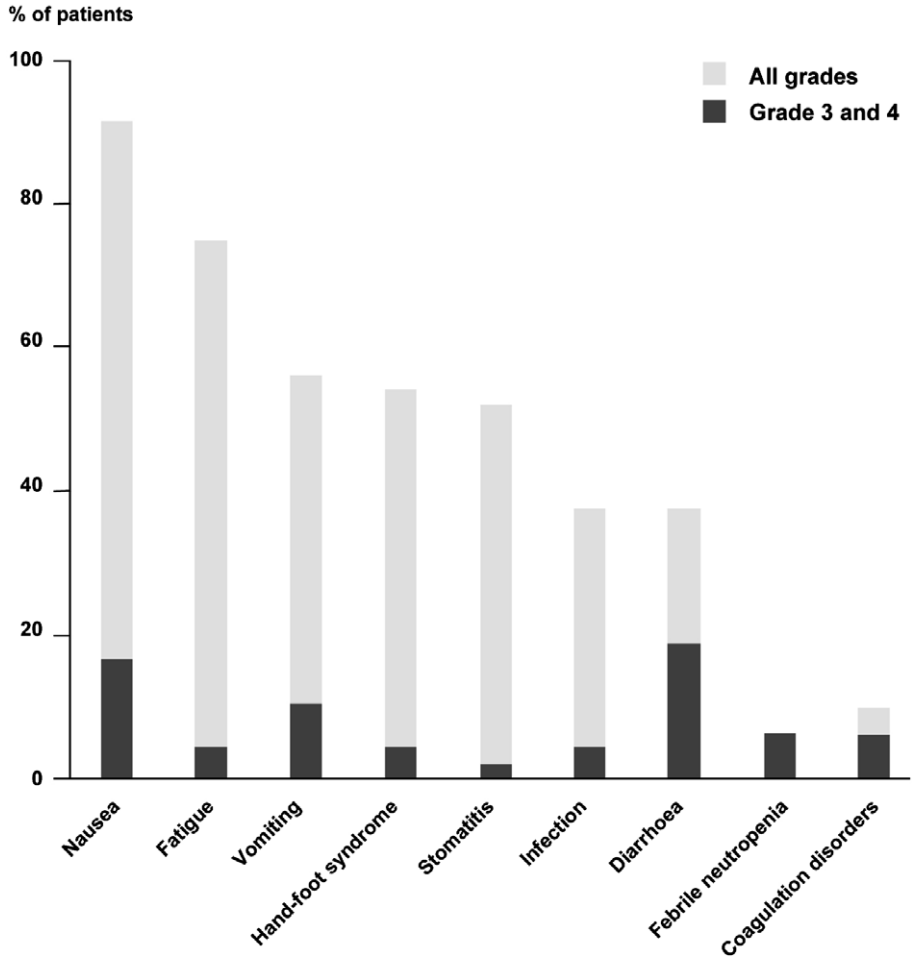


Fig. 2 – Most common treatment-related adverse events.

of 25%, which is concordant with published data.[19] HER2 amplification analysed by PCR was not predictive of treatment benefit.

4. Discussion

Neoadjuvant chemotherapy is the standard of care in reasonably fit patients with LABC. Besides the primary goal for patients of rendering inoperable tumours resectable, neoadjuvant chemotherapy enables *in vivo* assessment of chemosensitivity and provides an opportunity to study predictors of response. pCR is predictive of long-term survival in both LABC and operable breast cancer,[6,20] and therefore the continued search for new regimens yielding high pCR rate is important.

We demonstrated that neoadjuvant EXC is highly effective in LABC, with a clinical RR of 74% and a pCR rate of 22% (19% in the intent-to-treat population). Despite a diagnosis of LABC in all patients, rigorous criteria for pCR and administration of only four cycles of EXC, the pCR rate is similar to those with sequential anthracycline-/taxane-based primary chemotherapy (19–34%.[6,7]) It also compares favourably with pCR rates of 3–14% with dose-intensified anthracycline-based chemotherapy in LABC.[3,4] Furthermore, only one of nine patients achieving a pCR had relapsed after a median follow-up of 35 months. Consistent with previous findings,[21] survival was shorter in patients with IBC than in those with non-inflammatory LABC. High efficacy was demonstrated in this study despite inclusion of a high percentage (17%) of patients with IBC.

None of the biomarkers evaluated were predictive for outcome. This may have been because the study was not sufficiently powered to detect a difference. Secondly, both HER2 and the enzymes we investigated relate to only one component of the triplet regimen. Gene expression profiling has demonstrated that pCR is associated with changes in the expression of 80–90 genes,[22,23] highlighting the complexity of predicting response. Therefore it is likely that more sophisticated techniques will be required to predict response to EXC.

Two aspects of the safety profile of EXC in this study are of particular interest: chemotherapy-induced nausea and vomiting (CINV) and thrombogenic events. Although the incidence of grade 3/4 nausea and vomiting was initially of little concern, investigators reported that episodes of nausea were unusually protracted and posed a major problem. Consequently the protocol was amended, reducing the total number of cycles from eight to six and simultaneously a more aggressive anti-emetic scheme including dixyrazin and metoclopramide as well as $5HT_3$ receptor antagonists and steroids was also recommended. According to the investigators, patients treated prior to the protocol change had shown encouraging treatment responses and the rationale to continue the study was still strong and valid.

CINV was substantially less frequent in trials of EXC in oesophago-gastric and biliary tract carcinoma, including a randomised phase III trial (REAL-2) in patients with gastric cancer.[14,24–26] The all-female population in the present study compared with a predominance of males (63–88%) in the oesophago-gastric and biliary tract cancer studies may have contributed to the higher incidence of CINV, since female gender is an established risk factor for CINV.[27] The difference may also be due to the higher epirubicin dose and higher dose intensity delivered for all three drugs in the present study. In the REAL-2 trial[25] the capecitabine dose was 625 mg/m^2 twice daily without interruption, giving a slightly lower dose intensity than in the present study and in the other EXC trials.[14,24,26] In the present study, the dose of cisplatin, one of the most emetogenic cytotoxic compounds known, was maintained at almost 100% through all four neoadjuvant cycles, despite the high incidence of CINV. This suggests that, in some cases, cisplatin dose was not reduced appropriately. The relatively high number of patients withdrawn from the study because of toxicity rather than remaining on study treatment at a reduced dose also suggests that side effects were not always managed optimally. Since cisplatin is commonly used in gastric cancer but is rarely included in regimens for early breast cancer, earlier and more aggressive management of side effects in the gastric cancer trials may have contributed to the discrepancy in incidence of CINV. According to the recently published American Society of Clinical Oncology (ASCO) guideline on anti-emetic therapy in oncology, the two-drug combination of dexamethasone and aprepitant is recommended for the prevention of delayed emesis in all patients receiving cisplatin and other agents of high emetic risk.[28] Therefore, future studies evaluating the EXC regimen should include dexamethasone and aprepitant prophylaxis in the protocol.

The second side effect meriting further discussion is the possible thrombogenic properties of the EXC regimen, based on four cases of venous thrombosis in this study. In three of these patients, the event occurred after surgery. Increased risk of thromboembolism has not previously been attributed to capecitabine monotherapy[29] whereas 5-FU, the active metabolite of capecitabine, has been reported to increase the risk of thrombosis.[30] There is also some evidence of thrombogenic effects of both cisplatin[31] and epirubicin[32] and the possibility that EXC induces hypercoagulability cannot be eliminated. Chemotherapy-induced dehydration may also have contributed. No evidence of a significant increase in venous thromboembolic events was reported in the trials of oesophago-gastric and biliary tract carcinoma,[14,24,26] although in the study by Evans and colleagues, two cerebrovascular accidents occurred, but were considered attributable to co-existing vascular disease rather than drug toxicity.[14] Of note, increased incidence of thromboembolic events was reported with cisplatin-containing therapy compared with oxaliplatin-containing treatments in the large, randomised, phase III REAL-2 trial. However, this was unrelated to the use of i.v. 5-FU or capecitabine.[25]

Since completion of the present study, Smith and colleagues have published the 5-year analysis of a large, randomised, phase III trial in which patients with tumours of $\geqslant$3 cm diameter were randomised to receive either neoadjuvant epirubicin and cisplatin at the dose and schedule used in our study in combination with continuous infusion 5-FU (ECisF) or conventional bolus doxorubicin plus cyclophosphamide.[13] The ECisF regimen resulted in almost identical efficacy to the standard doxorubicin/cyclophosphamide regimen; the trend towards improved 5-year survival (82% with ECisF versus 74% with standard therapy; hazard ratio

0.76, $P = 0.18$) has not yet reached statistical significance. The efficacy results of our study are consistent with those reported for ECisF, with very similar clinical response and pCR rates. Interestingly, grade 3/4 nausea and vomiting occurred in 21% of patients receiving ECisF, similar to the rate seen in our study and significantly more common than in patients receiving standard therapy (10%, $P = 0.002$). Grade 3/4 thrombosis occurred in 17% of patients receiving ECisF compared with only 2% in the control arm ($P = 0.001$). Of note, 16% of patients receiving ECisF experienced grade 3/4 Hickman line infections, a problem that can be avoided by replacing continuous infusion 5-FU with oral capecitabine.

In conclusion, the EXC regimen showed high efficacy in LABC in terms of both RR and pCR rates. Nausea and vomiting were unexpectedly frequent, and more aggressive prophylaxis and management of these side effects is recommended to improve tolerability in future studies of this combination. Close monitoring for potential thrombogenic effects is advisable.

Conflict of interest statement

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