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Epirubicin and docetaxel with or without capecitabine as neoadjuvant treatment for early breast cancer: final results of a randomized phase III study (ABCSG-24)

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Background: This randomized phase III trial compared pathologic complete response (pCR) rates of early breast cancer (EBC) following neoadjuvant epirubicin–docetaxel (ED) ± capecitabine (C), and evaluated the addition of trastuzumab in HER2-positive tumors.

Patients and methods: Patients with invasive breast cancer (except T4d) were randomly assigned to receive six 3-weekly cycles of ED (both 75 mg/m^2) ± C (1000 mg/m^2, twice daily, days 1–14). Patients with HER2-positive disease were further randomized to receive trastuzumab (8 mg/kg, then 6 mg/kg every 3 weeks) or not. Primary end point: pCR rate at the time of surgery.

Results: Five hundred thirty-six patients were randomized to ED ($n = 266$) or EDC ($n = 270$); 93 patients were further randomized to trastuzumab ($n = 44$) or not ($n = 49$). pCR rate was significantly increased with EDC (23.0% versus 15.4% ED, $P = 0.027$), and nonsignificantly further increased with trastuzumab (38.6% EDC versus 26.5% ED, $P = 0.212$). Rates of axillary node involvement at surgery and breast conservation were improved with EDC versus ED, but not significantly; the addition of trastuzumab had no further impact. Hormone receptor status, tumor size, grade, and C (all $P \leq 0.035$) were independent prognostic factors for pCR. Trastuzumab added to ED ± C significantly increased the number of serious adverse events (35 versus 18; $P = 0.020$), mainly due to infusion-related reactions.

Conclusion: These findings show that the integration of C into a neoadjuvant taxane-/anthracycline-based regimen is a feasible, safe, and effective treatment option, with incorporation of trastuzumab in HER2-positive disease.

Clinical trial number: NCT00309556, www.clinicaltrials.gov.

Key words: capecitabine, docetaxel, early breast cancer, epirubicin, neoadjuvant treatment

introduction

Primary systemic chemotherapy (PST) is the treatment of choice for locally advanced, EBC, particularly when patients are not candidates for breast-conserving surgery (BCS) [1]. PST downstages the primary tumor and lymph node metastases [S1, S2] and increases opportunities for BCS. PST also allows early application of chemotherapy in a disease with a high distant failure rate and provides the opportunity for *in vivo* chemosensitivity testing of the primary tumor.

PST should comprise at least six cycles of an anthracycline- and taxane-containing regimen over 4–6 months [1]. We previously demonstrated that duration of therapy impacts on outcome; a significantly increased pathologic complete response (pCR) rate was observed with six versus three cycles of ED PST [2].

In large, randomized studies of PST, subgroup analyses have shown a correlation between pCR of the primary tumor and extended disease-free survival (DFS) or overall survival (OS) [3, S1, S3, S4]. This supports the conclusion that pCR of the

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primary tumor is a surrogate marker for eradication of micrometastases and improved survival, and identifies pCR as a primary goal of PST. Published data show pCR rates of 10%–15% with anthracycline-containing regimens [S1, S3], and <20% with anthracycline–taxane regimens [2, 4, 5].

While the addition of further cytotoxics to PST is generally limited by toxicity, capecitabine (C) has a favorable tolerability profile, which supports its use in combination strategies. As well as affording a survival benefit in metastatic breast cancer (MBC) as monotherapy [6], the combination of C with D demonstrated a survival benefit versus single-agent taxane in MBC [7]. The use of C in combination regimens is underpinned by preclinical evidence of its synergistic activity with a range of anticancer therapies, including D [S5]. The triple EDC combination was safe and efficacious in phase II evaluation in advanced/MBC [S6, S7].

The current study compared pCR rates after PST comprising ED or EDC in EBC, and evaluated the impact of the addition of trastuzumab to these regimens in patients with HER2-positive tumors.

patients and methods

study design

This prospective, randomized, multicenter, phase III trial compared ED ± C in EBC (www.clinicaltrials.gov; NCT00309556) (supplementary Figure S1, available at *Annals of Oncology* online). The use of trastuzumab was explored in HER2-positive tumors (immunohistochemistry 3+ and/or *HER2* gene amplification on fluorescence or chromogenic *in situ* hybridization).

The primary objective was the rate of pCR at the time of final surgery in patients receiving ED versus EDC; secondary objectives were the rate of axillary lymph node involvement at the time of final surgery and the rate of BCS in patients receiving ED versus EDC.

patients

Females aged 18–70 with histologically proven, core-biopsied, invasive breast cancer (except T4d) scheduled to receive preoperative chemotherapy were eligible. Patients were to have World Health Organization (WHO) performance status ≤2, no distant disease; no prior/current neoplasm (except curatively treated nonmelanoma skin cancer or *in situ* cervical cancer); and adequate left ventricular ejection fraction (LVEF; >50% lower normal limit) 4 weeks before study medication.

Patients with congestive heart failure or unstable angina pectoris, history of myocardial infarction within 1 year, uncontrolled hypertension/arrhythmias, or neuropathy ≥grade 2 were excluded. Patients who had undergone preoperative local treatment of EBC were ineligible, as were patients receiving concurrent corticosteroids, except when used for chronic treatment (initiated >6 months before study entry) at low dose (≤20 mg methylprednisolone or equivalent), or as inhalational agents, for prophylaxis, treatment of acute hypersensitivity reactions, or nausea/vomiting.

The study was conducted according to the principles of the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice. The protocol was approved by the appropriate Ethics Committees of each participating center before study initiation.

randomization

Patients were randomized via a computer program [S8] to receive six 3-weekly cycles of E 75 mg/m^2 plus D 75 mg/m^2 i.v., day 1, ±C 1000 mg/m^2 orally, twice daily, days 1–14. Patients with HER2-positive disease underwent a second randomization to receive trastuzumab (8 mg/kg i.v. day 1 cycle 1; 6 mg/kg subsequent cycles) or not. Premedication comprised dexamethasone 4–8 mg, days 0–2, and all patients received granulocyte colony-stimulating factors. Antiemetic prophylaxis was administered at the investigator's discretion. Treatment-related toxicity was managed by dose modification and supportive care.

Patients were stratified [S8] by: treatment center, stage (T1, T2, T3, T4a–c), axillary nodal status (positive, negative), menopausal status (pre, post), histology (invasive ductal, invasive lobular, mixed), hormone receptor (HR) status (positive [estrogen receptor (ER)+/progesterone receptor (PR)+, ER+/PR−, ER−/PR+], negative [ER−/PR−], unknown]), HER2 status (positive, negative, unknown), and grade (G1/G2, G3, not determinable [GX]). ER positivity was defined as ≥10% of cells stained positive.

Sentinel node biopsies were not permitted. Patients underwent BCS or modified radical mastectomy, with full axillary lymph node clearance, 3–5 weeks after the first day of the last chemotherapy cycle. At least eight lymph nodes had to be examined and described. BCS was attempted whenever possible. In case of clinically and/or radiologically confirmed progression the patient underwent salvage surgery. No second-line PST was allowed.

assessments

Adverse events (AEs) were classified according to WHO criteria. Hematologic, renal, and hepatic function was assessed after each cycle and at the end of therapy; LVEF was determined after cycle 3 and at the end of therapy.

Tumor and axillary nodal status was evaluated on day 1 of each cycle. Mammography and sonography of the tumor-bearing breast were carried out after cycle 3 and at the end of therapy. A pCR was defined as the absence of invasive tumor in the final surgical breast sample (stage yT0 or ypTis), according to the local pathologist, irrespective of nodal status. Specimens judged as pCR were reviewed centrally by a reference pathologist. All pathologists were blinded to treatment.

statistical analysis

Overall, 536 patients (5% drop-out rate for 510 eligible patients) were required to detect a pCR rate of 16% (ED) versus 27% (EDC) with a power of 83.3% at a significance level of 0.05 (two-sided χ^2 test). The study was to include 94 patients with HER2-positive disease to detect a pCR rate of 20% (ED ± C) versus 50% (ED ± C plus trastuzumab) with a power of 80.1% at a significance level of 0.05 (two-sided χ^2 test).

Based on a pCR rate of 18.6% with six cycles of ED [2], we selected an odds ratio (OR) of 1.5 to yield a pCR rate of 27% when a third drug was incorporated. For the HER2-positive subgroup, the OR of 2.667 [8] was applied, giving an expected pCR rate of 50%.

All randomized patients were included in the intent-to-treat analysis. Logistic regression analyses were carried out for determination of prognostic factors. Treatment effects were described by OR and 95% confidence intervals (CI).

A *post hoc* analysis assessed total pCR (absence of invasive tumor in the breast and axillary nodes) in all patients, and in the HER2-positive and triple-negative (TNBC) populations. In 2009, when TNBC was determined to have high sensitivity to chemotherapy, the steering group agreed to conduct *post hoc* analyses on this patient subgroup.

results

patients

From 2004 to 2008, 536 patients were enrolled and randomized to receive ED ($n = 266$) or EDC ($n = 270$) (Figure 1). Of 125 patients with HER2-positive tumors, 93 were randomized to receive trastuzumab ($n = 44$) or not ($n = 49$). Baseline

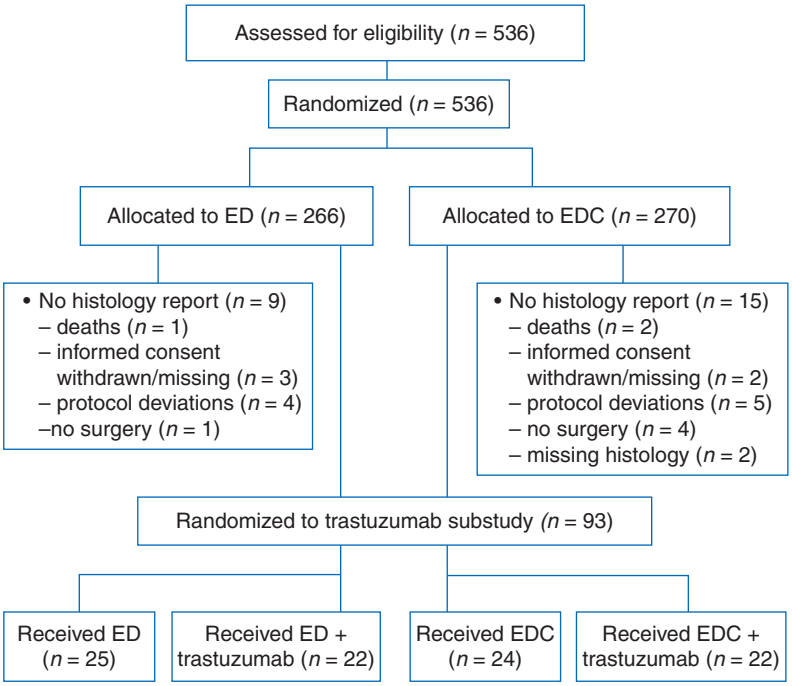

Figure 1. CONSORT diagram of patient flow through the study. C, capecitabine; ED, epirubicin–docetaxel.

Table 1. Response to ED ± C primary systemic therapy

n (%)	Total population (*N* = 536)			HER2-positive population (*N* = 93)			HER2-negative population (*N* = 400)		
	ED (*n* = 266)	EDC (*n* = 270)	*P*	ED ± C (*n* = 49)	ED ± C+T (*n* = 44)	*P*	ED (*n* = 200)	EDC (*n* = 200)	*P*
ypCR									
All patients	41 (15.4)	62 (23.0)	0.027	13 (26.5)	17 (38.6)	0.212	26 (13.0)	40 (20.0)	0.059
TNBC	19 (30.2)	29 (45.3)	–	–	–	–	–	–	–
Non-TNBC[a]	15 (8.3)	23 (12.5)	–	–	–	–	–	–	–
Axillary nodal status									
Negative	134 (50.4)	154 (57.0)	0.122	31 (63.3)	27 (61.4)	0.850	104 (52.0)	106 (53.0)	0.841
Positive	132 (49.6)	116 (43.0)		18 (36.7)	17 (38.6)		96 (48.0)	94 (47.0)	
Surgical procedure									
BCS	192 (72.2)	201 (74.4)	0.554	37 (75.5)	29 (65.9)	0.309	145 (72.5)	147 (73.5)	0.822
Mastectomy	74 (27.8)	69 (25.6)		12 (24.5)	15 (34.1)		55 (27.5)	53 (26.5)	

[a]*Post hoc* analysis, not preplanned; patients with HER2-positive disease who received trastuzumab were excluded.
BCS, breast-conserving surgery; C, capecitabine; ED, epirubicin–docetaxel; HER2, human epidermal growth factor receptor-2; T, trastuzumab; TNBC, triple-negative breast cancer; ypCR, pathologic complete response.

demographics were generally well balanced (supplementary Table S1, available at *Annals of Oncology* online). Although tumor stage was not perfectly balanced in the HER2-positive subgroup, there were no significant differences between the treatment arms. The ED/EDC arms and the trastuzumab/no trastuzumab arms were well balanced with respect to known prognostic factors.

efficacy

EDC significantly increased pCR rates compared with ED (23.0% versus 15.4%, $P = 0.027$). In HER2-positive tumors, pCR rates increased further with the addition of trastuzumab to ED ± C (38.6% versus 26.5%, $P = 0.21$), but the difference between the arms was not significant (Table 1). *Post hoc* analyses of total pCR confirmed these results (supplementary Table S2, available at *Annals of Oncology* online).

Rates of axillary node involvement at surgery were lower with EDC than with ED, while rates of BCS were higher (Table 1). In HER2-positive tumors, the addition of trastuzumab to ED ± C did not decrease rates of axillary node involvement at surgery or increase rates of BCS. Mastectomy rates were increased in patients with HER2-positive disease receiving ED ± C plus trastuzumab (34.1% versus 24.5% ED ± C, $P = 0.31$), possibly due to the higher proportion of patients with T4 tumors in this subgroup.

prognostic factors

A logistic regression model in the total population ($n = 536$) identified HR status ($P < 0.0001$), tumor stage ($P = 0.014$), grade ($P = 0.002$), and C therapy ($P = 0.035$) as independent prognostic factors for pCR (supplementary Table S3, available at *Annals of Oncology* online). A *post hoc* analysis identified TNBC status as an independent prognostic factor. Patients with TNBC had a significantly greater chance of achieving a pCR than non-TNBC (37.8% versus 10.4%, respectively; OR 5.23, 95% CI 3.20–8.55, $P < 0.0001$), irrespective of the chemotherapy used (interaction between treatment and TNBC: $P = 0.704$).

toxicity

Most patients (96% ED and 94% EDC) completed all six treatment cycles. The incidence of grade 3/4 AEs was significantly higher with EDC than ED ($P < 0.0001$; Table 2), mainly due to blood and lymphatic system and skin and subcutaneous disorders. Grade 3 hepatobiliary disorders and nervous system disorders were more frequent with EDC than ED ($P < 0.05$). The addition of trastuzumab did not significantly increase the incidence of grade 3/4 AEs ($P = 0.526$).

Serious AEs (SAEs) were more frequent with EDC (135 versus 94 events ED, $P = 0.007$; supplementary Table S4, available at *Annals of Oncology* online), largely due to neutropenia and capecitabine-related gastrointestinal toxicity. Although the incidence of vascular SAEs was low, they were more common with EDC than with ED. Two were defined as SAEs on the basis of hospital admission (no thrombosis found). Six were thromboembolic events in the lower extremities ($n = 5$) or in association with an implanted venous access system ($n = 1$); five of these occurred in markedly overweight or clinically obese patients.

The addition of trastuzumab to ED ± C significantly increased the incidence of SAEs (35 versus 18 events, respectively; $P = 0.020$), mostly due to infusion-related reactions. There were no significant differences in the rates of SAEs attributable to hematologic, cardiologic, or neurologic toxicities.

Three deaths occurred: two with ED (suicide and pulmonary embolism following PST and surgery), and one with EDC (cause unidentified).

discussion

The addition of C to ED increased pCR rates from 15.4% to 23.0% ($P = 0.027$) in this randomized phase III study. Although intertrial comparisons must be interpreted with caution, the pCR rate was ≥20% in HER2-negative and -positive tumors and

Table 2. Grade 3/4 AEs occurring in >5 patients in either treatment group

System organ class, *n* preferred term	WHO grade	Total population ($N = 526$)			HER2-positive population ($N = 91$)		
		ED ($n = 93$)	EDC ($n = 140$)	*P*	ED ± C ($n = 25$)	ED ± C + T ($n = 21$)	*P*
Blood and lymphatic system disorders	G3	71	161	<0.0001	26	18	0.29
	G4	43	91	<0.0001	11	14	0.69
Cardiac disorders	G3	0	0	1.00	2	2	1.00
	G4	0	0	1.00	0	3	0.25
Cardiac failure	G3	0	0	1.00	1	0	1.00
	G4	0	0	1.00	0	0	1.00
Left ventricular dysfunction	G3	0	0	1.00	1	1	1.00
	G4	0	0	1.00	0	2	0.50
Diastolic dysfunction	G3	0	0	1.00	0	1	1.00
	G4	0	0	1.00	0	1	1.00
Gastrointestinal disorders[a]	G3	24	46	0.012	6	9	0.79
	G4	6	7	1.00	1	1	1.00
General and administration site disorders	G3	11	19	0.201	1	0	1.00
	G4	0	2	0.500	0	1	1.00
Hepatobiliary disorders	G3	1	11	0.006	4	0	0.125
	G4	1	0	1.00	0	0	1.00
Transient hyperbilirubinemia	G3	1	9	0.022	0	0	1.00
	G4	0	0	1.00	0	0	1.00
Infections and infestations	G3	7	9	0.80	3	3	1.00
	G4	1	3	0.625	0	0	1.00
Metabolism and nutrition disorders	G3	4	8	0.388	2	1	1.00
	G4	1	1	1.00	1	0	1.00
Nervous system disorders	G3	4	13	0.049	2	2	1.00
	G4	0	0	1.00	0	0	1.00
Skin and subcutaneous tissue disorders	G3	0	23	<0.0001	5	1	0.219
	G4	0	11	0.001	0	2	0.50

[a]Includes mucositis, stomatitis, diarrhea, nausea, and vomiting.

AE, adverse event; C, capecitabine; ED, epirubicin-docetaxel; HER2, human epidermal growth factor receptor-2; T, trastuzumab; WHO, World Health Organization.

compares favorably with other PST regimens [2–5]. Such comparison is, however, compromised by the varying definitions of pCR used in these trials.

The benefit observed with the addition of C is in accordance with the OS benefit observed with the addition of C to D in MBC [7], and with the addition of C to an anthracycline-containing regimen in the USON01602 adjuvant trial [9]. Adjuvant C, however, was inferior to standard adjuvant chemotherapy in elderly women with EBC [10].

Our results contrast with the GeparQuattro [11] and NSABP B-40 studies [12], where addition of C did not increase pCR rates. However, in both trials, C was used at a lower dose, and C and D were administered for only four cycles. Also, we used similar doses of E and D in both treatment arms, whereas GeparQuattro employed a lower D dose in the experimental versus the control arm. These factors may have contributed to the lack of significant benefit observed. Indeed, guidelines recommend at least six cycles of PST over 4–6 months [1].

The benefit afforded by the addition of trastuzumab to chemotherapy in HER2-positive disease has been demonstrated in MBC and EBC [13, 14]. The synergism between taxanes and trastuzumab further supports the combination of these agents [15]. In our study, the addition of trastuzumab did not significantly improve pCR rates in HER2-positive tumors, possibly due to the small size of the subgroup. In study ABCSG-14, we observed a 2.6-fold increased chance of pCR following six cycles of ED without trastuzumab in patients with HER2-positive versus HER2-negative tumors [2].

Similar results to ours were reported in a randomized trial evaluating the addition of trastuzumab to four cycles of FEC [16], with a pCR rate of 65.2% with trastuzumab versus 26.0% without ($P = 0.016$). Although the study was terminated early, longer-term follow-up confirmed the favorable outcome of patients receiving trastuzumab, with 1- and 3-year DFS rates of 100% ($P = 0.041$).

Hormone receptor status, tumor stage, grade, and C therapy were independent prognostic factors for pCR. The addition of C to ED resulted in a 1.64-fold increase in the possibility of pCR, and small tumors, HR-negative disease, and undifferentiated (G3) tumors were associated with a 2.4-, 4.3-, and 2.5-fold increased chance of pCR after treatment with ED or EDC, respectively. Based on our data, the addition of C to ED appears to be highly effective in inducing a pCR in undifferentiated (G3) tumors and in ER- and PR-negative tumors. In particular, triple-negative tumors reached a pCR rate of 45.3%. Thus, further neoadjuvant studies should focus on TNBC, which are mostly G3.

Limitations of our study include the small sample size of the HER2-positive subgroup, the lack of a prospectively defined subgroup of TNBC patients, the absence of biomarker data, and the fact that the backbone regimen is not internationally used. However, this large, prospective trial utilized rigorous methodology, with a randomized, multicenter design that prohibited the use of second-line PST to prevent any impact on the primary end point.

Capecitabine added to the toxicity of ED, with an increased rate of grade 3/4 AEs and SAEs; severe myelotoxicity was not significantly increased with EDC, consistent with the established safety profile of C [6]. The low treatment discontinuation rates further support the favorable tolerability of EDC. The addition of trastuzumab to ED ± C significantly increased the incidence of SAEs, but these were almost exclusively infusion-related reactions. In common with other studies [8, 16, 17], the addition of trastuzumab was not associated with cardiac toxicity.

In conclusion, these data show that the integration of C into taxane-/anthracycline-based PST is a feasible, safe, and effective treatment option, with incorporation of trastuzumab for HER2-positive tumors. It remains unclear whether the addition of C to PST is indeed the optimal treatment approach; additional studies or meta-analyses may help to answer this question. Our data also suggest that a set of biological markers, rather than single markers, is required to differentiate between a high or low chance for pCR following PST.

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disclosure

GGS has received research support and consultancy fees from Roche Austria and Amgen, lecture fees, advisory board fees, travel grants, and meeting grants from Amgen, Roche Austria, Hoffmann La-Roche, Sanovi-Aventis, AstraZeneca, GlaxoSmith Kline, Novartis, Cephalon, and Eisai, and lecture fees from EBEWE and Pfizer. RG has received research grants from Roche Austria, Amgen, EBEWE, and Sanofi. AL has received travel grants from Amgen and Roche Austria, lecture fees from Roche-Austria, and advisory board fees from Sanofi-Aventis. FF has received meeting grants from Amgen, Roche Austria, Sanofi-Aventis, and EBEWE. BM has received travel grants from Amgen and Roche Austria, and advisory board fees from Amgen. BLH has received travel grants from Roche Austria. RB has received lecture fees from Roche Austria, Amgen, and Sanofi-Aventis, and travel grants from Roche Austria. MH has received travel grants from Amgen and Roche Austria. HS has received lecture fees and travel grants from Amgen, Roche Austria, and Sanofi-Aventis. PD has received travel grants from Roche Austria, and lecture fees from Amgen. ALP has received research grants from Roche Austria, lecture fees and advisory

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