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ORIGINAL REPORT

Randomized, Phase III Trial of Sequential Epirubicin and Docetaxel Versus Epirubicin Alone in Postmenopausal Patients With Node-Positive Breast Cancer

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ABSTRACT

Purpose
The Docetaxel Epirubicin Adjuvant (DEVA) trial evaluated the efficacy and toxicity of incorporating docetaxel after epirubicin to create a sequential anthracycline-taxane regimen in early breast cancer.

Patients and Methods
After complete tumor excision, postmenopausal women with node-positive early breast cancer were randomly assigned to either epirubicin 50 mg/m^2 on days 1 and 8 every 4 weeks for six cycles (EPI × 6) or three cycles of epirubicin 50 mg/m^2 on days 1 and 8 every 4 weeks followed by three cycles of docetaxel 100 mg/m^2 on day 1 every 3 weeks (EPI-DOC). A subset of patients also participated in a quality of life (QOL) study. The primary end point was disease-free survival (DFS).

Results
From 1997 to 2005, 803 patients entered DEVA (EPI × 6, n = 397; EPI-DOC, n = 406). At a median follow-up of 64.7 months (interquartile range, 45.2 to 84.4 months), 198 DFS events had been reported (EPI × 6, n = 114; EPI-DOC, n = 84). The 5-year DFS rates were 72.7% (95% CI, 68.0% to 77.3%) for epirubicin alone and 79.5% (95% CI, 75.2% to 83.8%) for epirubicin followed by docetaxel; evidence of improvement in DFS was observed with EPI-DOC (hazard ratio [HR], 0.68; 95% CI, 0.52 to 0.91; $P = .008$). One hundred twenty-seven patients have died (EPI × 6, n = 75; EPI-DOC, n = 52); a reduction in deaths was observed with EPI-DOC (HR, 0.66; 95% CI, 0.46 to 0.94; $P = .02$). The 5-year overall survival rates were 81.8% (95% CI, 77.7% to 85.9%) for epirubicin and 88.9% (95% CI, 85.5% to 92.2%) for epirubicin followed by docetaxel. Assessment of toxicity and QOL showed that EPI-DOC was associated with greater toxicity but with no difference in QOL between arms during follow-up.

Conclusion
These results suggest, within a relatively small trial, that substitution of docetaxel for epirubicin for the last three cycles of chemotherapy results in improved outcome in postmenopausal women with node-positive, early breast cancer compared with six cycles of epirubicin monotherapy.

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INTRODUCTION

Breast cancer is the most common cancer in women in the developed world. Adjuvant systemic therapy has been shown to improve survival in patients with localized early breast cancer. In 1998, when the Docetaxel Epirubicin Adjuvant (DEVA) trial was being developed, the global evidence regarding adjuvant cytotoxic chemotherapy had been summarized by the Early Breast Cancer Trialists' Collaborative Group,[1] including a comparison of anthracycline-containing chemotherapy with regimens of cyclophosphamide, methotrexate, fluorouracil (CMF) showing that, overall, the addition of an anthracycline improved both disease-free survival (DFS) and overall survival (OS). At this time, a concern existed that the adverse events of anthracycline-containing chemotherapy in postmenopausal patients could outweigh the benefits.

We had previously conducted a study (ie, Epirubicin Plus Tamoxifen Versus Tamoxifen Alone, or Epi-Tam) in postmenopausal patients with early breast cancer[2] to test whether the addition of single-agent anthracycline to tamoxifen could improve DFS when compared with tamoxifen alone for 4 years. The results supported this hypothesis, with a 28% relative improvement in DFS with epirubicin (hazard ratio [HR], 0.72; 95% CI, 0.54 to 0.96; $P = .02$) that suggested that anthracycline therapy was of benefit in postmenopausal patients with early breast cancer.

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At the time that the Epi-Tam trial was reported, taxanes had emerged as active cytotoxics in metastatic breast cancer, particularly in patients resistant to anthracyclines.[3] Concern about adverse effects was raised again, however, by clinicians reluctant to subject patients to potential neurologic adverse effects associated with taxanes. In 2000, the National Institutes of Health consensus panel concluded that the evidence for taxanes in node-positive patients was inconclusive[4] and called for additional research. DEVA was established against this background to compare single-agent anthracycline chemotherapy with a sequential anthracycline-taxane regimen.

Some issues concerning tamoxifen use were debated in the late 1990s. Early Breast Cancer Trialists' Collaborative Group had concluded that a small but significant benefit of tamoxifen had been reported in patients with estrogen receptor (ER) –negative tumors[5]; however, there was uncertainty about the timing of tamoxifen because of a negative interaction between cytotoxic chemotherapy and tamoxifen[6] and because of an increase in thromboembolic events in patients who had received concurrent chemotherapy and tamoxifen.[7]

The primary aim of DEVA, however, was to evaluate the efficacy of sequential chemotherapy with epirubicin followed by docetaxel (ie, EPI-DOC) compared with epirubicin alone (EPI × 6) in postmenopausal patients with node-positive breast cancer.

PATIENTS AND METHODS

Study Design

DEVA is a multicenter, phase III, randomized controlled trial with partial 2 × 2 factorial design. Patients were randomly assigned in a 1:1 ratio to EPI × 6 or EPI-DOC. An optional second random assignment of the timing of tamoxifen treatment commencing either concurrently or sequentially with chemotherapy was carried out in a subset of 13 centers. This will be reported separately. Initially, tamoxifen was prescribed irrespective of ER/progesterone receptor status, and centers that opted out of the tamoxifen random assignment were to administer tamoxifen concurrently. The protocol was amended in 2001 so that tamoxifen could be omitted for ER/progesterone receptor–negative patients and in 2007 to allow use of aromatase inhibitors after positive results in aromatase inhibitor trials.[8,9]

Patients

This study was undertaken in 36 centers in five European countries. Eligible patients were postmenopausal women with node-positive invasive early breast cancer who had undergone complete tumor excision. Postmenopausal status was defined by either last menstrual period greater than 12 months before surgery, women who had a bilateral oophorectomy, or age ≥ 50 years and women who had a hysterectomy. All patients must have been deemed fit for treatment with chemotherapy and were required to have normal hematologic, hepatic, and renal function, with no evidence of cardiac disease as assessed by ECG and/or left ventricular ejection fraction (LVEF) estimation. LVEF had to be within each institutional range of normal as measured by multigated acquisition scan. Patients with distant metastases or a history of a previous or concomitant malignancy were excluded. All patients gave written informed consent before taking part.

Random Assignment

Independent random assignment was by telephone/fax to the International Collaborative Cancer Group Data Centre, London, United Kingdom. Computer-generated permuted blocks were used; stratification was by center and intention to treat with tamoxifen (elected/randomized or concurrent/sequential/none).

Procedures

All treatments administered in the trial were open label. The EPI × 6 group received epirubicin 50 mg/m^2 administered on days 1 and 8 every 4 weeks for six cycles. The EPI-DOC group consisted of epirubicin administered for three cycles as above followed by three cycles of docetaxel (Taxotere; sanofi-aventis, Paris, France) 100 mg/m^2 administered as a 1-hour infusion on day 1 of a 3-week cycle with dexamethasone 8 mg orally twice daily for 3 days.

Dose modifications and/or delays for chemotherapy were based on treatment-day hematologic and liver toxicity. Treatment delays were allowed up to a maximum of 2 weeks. If the toxicity did not resolve within 2 weeks, treatment was discontinued. The use of prophylactic granulocyte colony-stimulating factor and antibiotics was recommended in the case of febrile neutropenia. Chemotherapy was discontinued for any episode of sepsis or in the event of cardiotoxicity (ie, cardiac symptoms, ECG abnormalities, or LVEF > 15% less than the lower limit of normal for the institution) or grade 4 hepatotoxicity.

Tamoxifen (20 mg once daily), if given, was administered either at the beginning (concurrent) or end (sequential) of chemotherapy. Adverse events were assessed at the end of each chemotherapy cycle, with follow-up every 3 months for the remainder of year 1, every 4 months in year 2, every 6 months for years 3 and 4, and annually thereafter up to a minimum of 10 years. Clinical adverse events and changes were assessed according to the National Cancer Institute Common Toxicity Criteria (version 2)[10] and were coded by using the Medical Dictionary for Regulatory Activities (MedDRA, version 10.0).[11]

End Points

The primary end point of the study was DFS, defined as time to locoregional recurrence (ie, ipsilateral breast or axillary node relapse), distant recurrence, new primary breast cancer (ie, contralateral breast cancer) or death as a result of any cause; patients who remained alive and disease free at their last follow-up were censored at that date. Secondary end points were OS; breast cancer–free survival (BCFS) defined to end with breast cancer death; contralateral breast cancer; local recurrence or metastases with time censored at non–breast cancer death; and metastasis-free survival (MFS) defined to end with metastases, breast cancer death, or death as a result of unknown cause, with time censored at other death. The time to any event was measured from date of random assignment. When cause of death was unknown, these events were classed conservatively as breast cancer deaths. Treatment-related deaths were those that occurred within 30 days of finishing trial treatment.

The planned primary end point for the tamoxifen random assignment was incidence of thromboembolic events during the first 9 months after random assignment. However, it was recognized at the outset that a larger number of patients would be required to explore the impact on disease outcome for patients treated by these two methods: concurrently or sequentially. Therefore, it was expected that data would be available for inclusion with that from other randomized trials in a large meta-analysis.

Statistical Justification for Sample Size and Analyses

Sample size was determined with the SampSize software (http://sampsize.sourceforge.net)[12] by using the 1982 Freedman[13] approximation of sample size/power calculation on the basis of the log-rank test. It was calculated that the trial required 792 patients, providing 90% power (α = .05) to detect an improvement in 5-year DFS from 70% for EPI × 6 to 80% for EPI-DOC. No adjustment was made for accrual rate or potential loss to follow-up in the sample size. All analyses were conducted according to the intention-to-treat principle, and $P < .05$ was deemed statistically significant unless otherwise stated.

Time-to-event analyses were conducted with Kaplan-Meier plots that graphically depicted survival functions and with log-rank tests that provided a comparison between treatment groups. HRs were determined with Cox proportional hazards regression analysis both univariately and after adjustment for selected prognostic factors, for which values less than 1 favored EPI-DOC. Comparison of treatment groups for toxicity was made with the χ^2 test, t test, or Mann-Whitney U test, as appropriate, and was analyzed by treatment actually received. $P < .01$ was deemed statistically significant for toxicity analyses to allow some adjustment for multiple testing. SPSS 16.0.2 (SPSS, Chicago, IL) and Stata 10.1 (STATA, Santa Monica, CA) statistical packages were used.

Quality of Life Substudy

The quality of life (QOL) study aimed to evaluate individual physical, psychological, and social factors relating to patient well-being and aimed to

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provide an overall Global Health Status score by using the validated European Organisation for Research and Treatment of Cancer (EORTC) core Quality of Life Questionnaire C30 (QLQ-C30) and the breast cancer–specific Quality of Life Questionnaire BR23 (QLQ-BR23) module; both are patient self reported. The study was carried out in a limited number of centers (and intention to participate was recorded centrally before first random assignment). Data were collected at baseline, 9 months, 2 years, and 5 years after random assignment; questionnaires were completed while patents were in clinic. Analysis of covariance was performed by using baseline values as the covariate; to take account of multiple testing, $P = .01$ was used to indicate significance. A higher mean score represents a better result in the Functional scales but a worsening of symptoms in the Symptom scales.

Trial Management

DEVA was approved by the London Multi-Research Ethics Committee (MREC/99/2/1) and by local ethics committees of all participating centers. The International Collaborative Cancer Group Data Centre, Imperial College London, United Kingdom, had overall responsibility for trial coordination. The trial database was held at the Clinical Trials and Statistics Unit at The Institute of Cancer Research, Sutton, United Kingdom, which was also responsible for statistical analyses. The trial Steering Committee was responsible for trial oversight. Emerging safety and efficacy data were reviewed by an independent data monitoring committee. The sponsor was Imperial College London, and the trial is on the International Standard Randomized Controlled Trial Register as ISRCTN89772270.

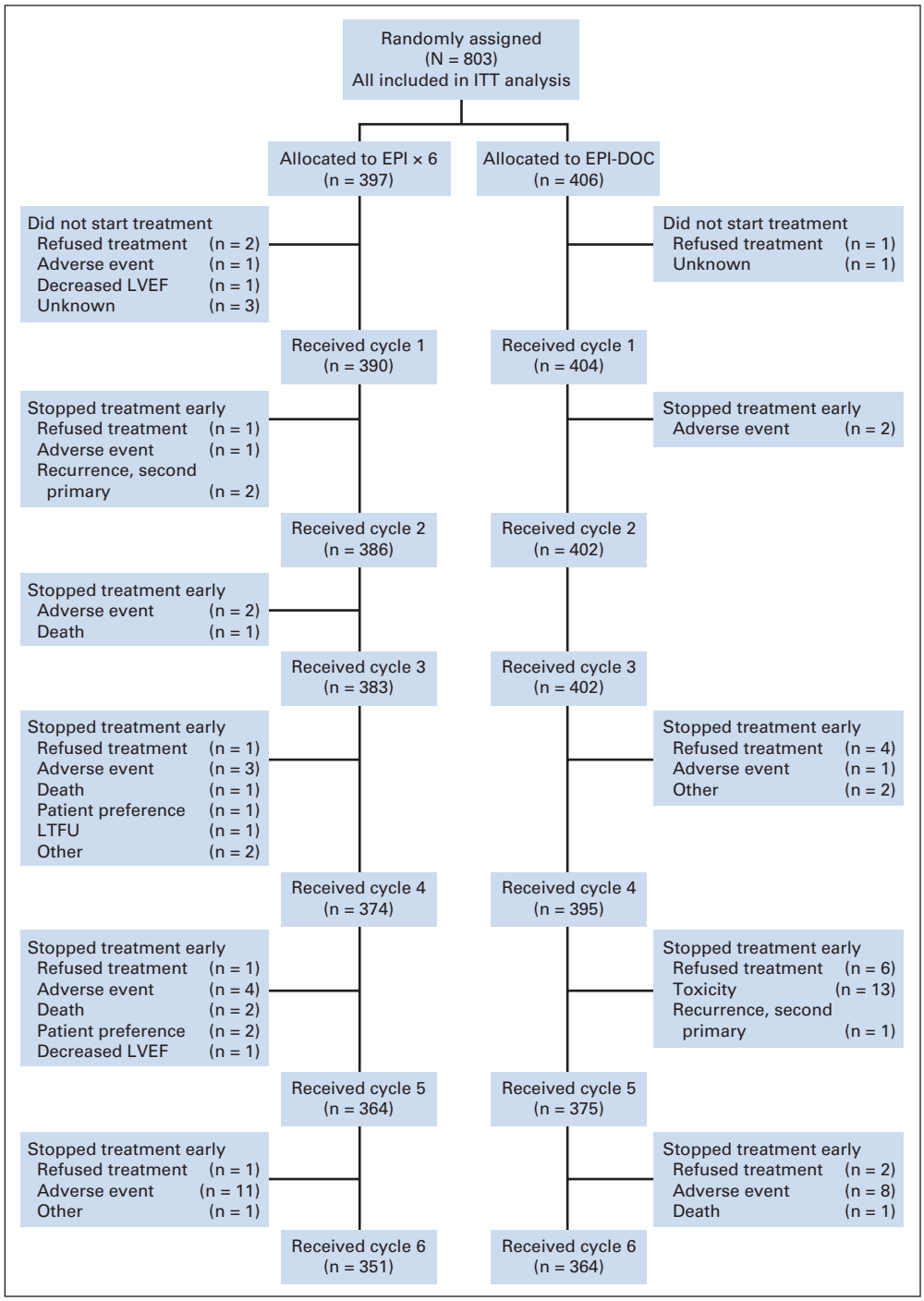

Fig 1. CONSORT diagram. Screening data was not routinely collected when this study was initiated and therefore was not included in the CONSORT diagram. ITT, intention to treat; EPI × 6, six cycles of epirubicin; EPI-DOC, three cycles of epirubicin followed by three cycles of docetaxel; LVEF, left ventricular ejection fraction; LTFU, long-term follow-up.

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RESULTS

Between 1997 and 2005, a total of 803 patients (EPI × 6, n = 397; EPI-DOC, n = 406) entered DEVA (Fig 1). At the time of this analysis, median follow-up in all patients was 64.7 months (interquartile range, 45.2 to 84.4 months). Six patients were ineligible; four had no evidence of node involvement, and two had reduced LVEF at initial assessment. Only one patient withdrew consent for additional treatment and follow-up (in the EPI-DOC arm), and approximately 3% were classified as lost to follow-up; all patients were included in the intention-to-treat analyses.

Baseline clinicopathologic characteristics of patients were evenly balanced between treatment groups (Table 1), including histologic subtype (not shown). Treatment compliance was good, with 88.4% of patients receiving all six cycles of EPI × 6 and 89.7% receiving all six cycles of EPI-DOC. The principal reason for early discontinuation was toxicity. Overall, 91.9% of the EPI × 6 group and 94.6% of the EPI-DOC group received at least 85% of their planned dose-intensity for cycles 1 to 3; these results were reduced to 84.1% in the EPI × 6 group and 76.1% in the EPI-DOC group for cycles 4 to 6.

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Treatment Arm: EPI × 6 (n = 397) No.	%	EPI-DOC (n = 406) No.	%	Total (N = 803) No.	%
Age, years						
< 50	11	2.8	12	2.9	23	2.9
50-59	194	48.9	191	47.0	385	47.9
60-69	163	41.1	175	43.1	338	42.1
70-79	29	7.3	28	6.9	57	7.1
Type of surgery						
Mastectomy	203	51.1	207	51.0	410	51.1
Wide local excision	181	45.6	187	46.1	368	45.8
Other	10	2.5	11	2.7	21	2.6
Not known	3	0.8	1	0.2	4	0.5
Side of primary						
Left	188	47.6	176	43.1	364	45.3
No. with radiation therapy	159		134		293	
Right	161	40.6	184	45.3	345	43.0
No. with radiation therapy	123		151		274	
Not known	48	12.1	46	11.3	94	11.7
No. with radiation therapy	32		36		68	
Tumor grade						
1	54	13.7	42	10.3	96	12.0
2	172	43.3	181	44.6	353	44.0
3	129	32.5	148	36.5	277	34.5
Not known	42	10.6	35	8.6	77	9.5
Nodal status						
Negative	1	0.3	3	0.7	4	0.5
Positive						
No. of nodes						
1-3	266	67.0	265	65.3	531	66.1
≥ 4	125	31.5	135	33.3	260	32.4
Not known	5	1.3	3	0.7	8	1.0
Tumor size, cm						
≤ 2	184	46.3	172	42.4	356	44.3
2-5	186	46.9	206	50.7	392	48.8
> 5	24	6.0	27	6.7	51	6.4
Not known	3	0.8	1	0.2	4	0.5
Hormone receptor status						
ER and/or PR positive	309	77.8	313	77.1	622	77.5
ER and PR negative	75	18.9	82	20.2	157	19.5
ER and PR not known	13	3.3	11	2.7	24	3

Abbreviations: EPI × 6, six cycles of epirubicin; EPI-DOC, three cycles of epirubicin followed by three cycles of docetaxel; ER, estrogen receptor; PR, progesterone receptor.

Tamoxifen Administration and Related Toxicities

Three hundred seventy-eight patients were entered into the timing of tamoxifen random assignment (concurrent tamoxifen, n = 189; sequential tamoxifen, n = 189). The treatment groups were well balanced in relation to both any-grade and grades 3 to 4 toxicities (data not shown), and there was similar frequency in overall occurrence of thromboembolic events in the two groups (concurrent tamoxifen, n = 19; sequential tamoxifen, n = 15). In addition, an additional 316 patients were elected to have concurrent tamoxifen, and 91 patients were elected to have sequential tamoxifen; 18 patients were elected to no tamoxifen treatment. Of the 785 patients randomly assigned or elected to receive concurrent or sequential tamoxifen, 604 (77%) received tamoxifen per protocol, and 121 (15%) did not receive tamoxifen at any time. Aromatase inhibitors were taken by 33 (4%) of 803 patients (EPI × 6, n = 18; EPI-DOC, n = 15); 28 of these 33 patients received anastrozole, and five received letrozole.

Efficacy

In total, 198 DFS events (all nonstandardized efficacy end points [non-STEEP] events) have been reported (EPI × 6, n = 114; EPI-DOC, n = 84; Table 2). An improvement in DFS was seen for EPI-DOC compared with EPI × 6 (unadjusted HR, 0.68; 95% CI, 0.52 to 0.91; $P = .008$, Fig 2). The divergence in the curves seen after 6 months was observed for both ER-negative and ER-positive breast cancers. DFS analysis of standardized efficacy end points (STEEP), including

Table 2. DFS Events by Treatment Group As Non-STEEP Results

Type of DFS First Event	Treatment Arm: EPI × 6 (n = 397)	EPI + DOC (n = 406)	Total (N = 803)
Local recurrence	19	13	32
Distant relapse	74	63	137
Concurrent local and distant relapse	2	0	2
Breast second primary tumor	4	1	5
Breast cancer death (no recurrence)	2	0	2
Non–breast cancer death (no recurrence)	12*	7†	19
Unknown which event first	1	0	1
Overall events	114	84	198

Abbreviations: DFS, disease-free survival; EPI × 6, six cycles of epirubicin; EPI-DOC, three cycles of epirubicin followed by three cycles of docetaxel; non-STEEP, nonstandardized efficacy end points.

*Deaths were results of metabolic acidosis assumed to be a result of treatment, non–small-cell lung cancer, ovarian cancer, glioblastoma multiforme, metastatic gastric cancer, cardiac problem/kidney failure, cardiac event, aspiration pneumonia, myocardial infarction, unknown causes, and two congestive cardiac failures (at 6 and 9 years, respectively, after random assignment).

†Deaths were results of neuroendocrine carcinoma assumed to be a result of treatment, peritoneal carcinosis/ovarian cancer, cerebral hematoma, cardiac problems, unknown cause, and alcoholic hepatic cirrhosis.

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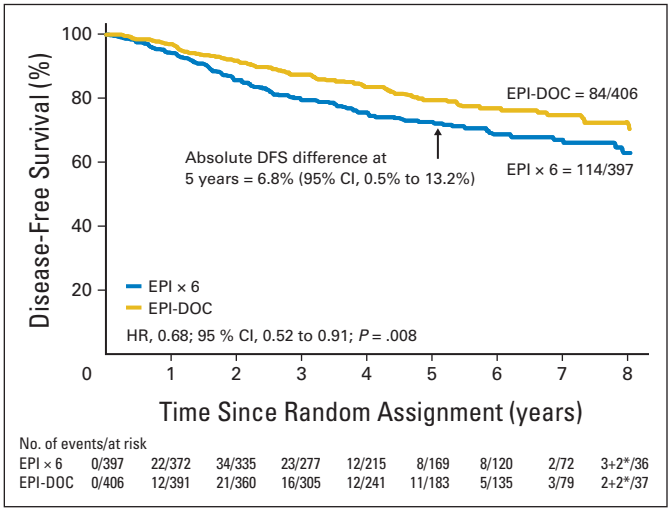

Fig 2. Disease-free survival in the ITT population (N = 803). (*) Number of events/at risk in events occurring after 8 years. DFS, disease-free survival; EPI × 6, six cycles of epirubicin; EPI-DOC, three cycles of epirubicin followed by three cycles of docetaxel; HR, hazard ratio.

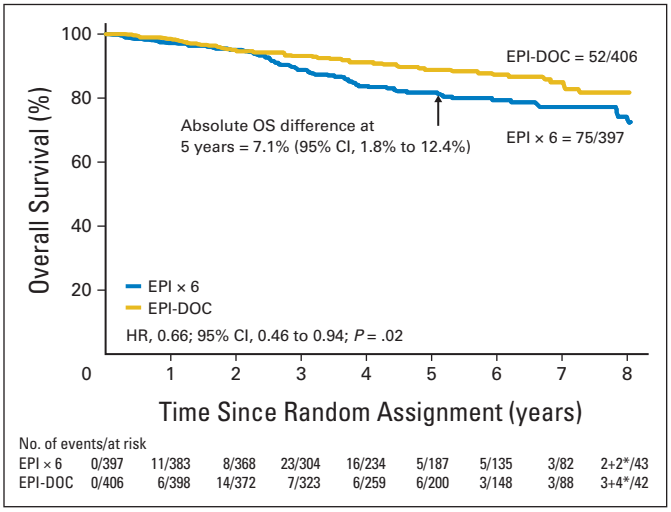

Fig 3. Overall survival in the ITT population (N = 803). (*) Number of events/at risk in events occurring after 8 years. EPI × 6, six cycles of epirubicin; EPI-DOC, three cycles of epirubicin followed by three cycles of docetaxel; HR, hazard ratio; OS, overall survival.

nonbreast second primaries, demonstrated a comparable improvement with EPI-DOC compared with EPI × 6 (unadjusted HR, 0.69; 95% CI, 0.52 to 0.90; $P = .007$). Nonbreast second primaries are shown in Table 3. The 5-year DFS rates were 72.7% for EPI × 6 (95% CI, 68.0% to 77.3%) and 79.5% for EPI-DOC (95% CI, 75.2% to 83.8%), which translated into a 5-year absolute improvement in DFS of 6.8% (95% CI, 0.5% to 13.2%) for EPI-DOC. Adjustment for known prognostic factors (ie, ER status [ER-positive or ER-negative], tumor grade [grade 1, 2, 3, or unknown], tumor size [≤ 2 cm, 2 to 5 cm, or >5 cm], and extent of node involvement [1 to 3, or ≥ 4]) gave an HR of 0.58 (95% CI, 0.43 to 0.79; $P < .001$). The human epidermal growth factor receptor 2 (HER2) status was not available in this study. Subgroup analyses show consistency with the overall effect (Appendix Fig A1, online only).

Table 3. Summary of Nonbreast Second Primary Tumors by Treatment Group

Type of Nonbreast Second Primary Tumor	Treatment Arm		Total (N = 21)
	EPI × 6 (n = 11)	EPI-DOC (n = 10)	
Skin cancer	1	2	3
Ovarian cancer	3	1	4
Lung cancer	1	2	3
Endometrial adenocarcinoma	1	1	2
Acute myeloid leukemia	1	0	1
Glioblastoma multiforme	1	0	1
Gastric adenocarcinoma	1	0	1
Rectum adenocarcinoma	1	0	1
Non-Hodgkin's lymphoma	0	2	2
Cervical cancer	1	0	1
Neuroendocrine carcinoma	0	1	1
Multiple myeloma	0	1	1

Abbreviations: EPI × 6, six cycles of epirubicin; EPI-DOC, three cycles of epirubicin followed by three cycles of docetaxel.

During a median follow-up of approximately 5 years, 127 patients (15.8%) have died (EPI × 6, n = 75; EPI-DOC, n = 52). One hundred seven deaths (EPI × 6, n= 62; EPI-DOC = 45) were as a result of breast cancer; 18 patients (EPI × 6, n = 12; EPI-DOC, n = 6) died with no evidence of relapse of breast cancer, and two (one in each treatment arm) died as a result of an unknown cause (Table 2). There was a statistically significant improvement in OS in favor of EPI-DOC (HR, 0.66; 95% CI, 0.46 to 0.94; $P = .02$), and the difference in survival began to appear within 3 years of random assignment (Fig 3). The 5-year survival rates were 81.8% (95% CI, 77.7% to 85.9%) for EPI × 6 compared with 88.9% (95% CI, 85.5% to 92.2%) for EPI-DOC, which provided an absolute difference in OS at 5 years of 7.1% (95% CI, 1.8% to 12.4%). BCFS and MFS both suggested improvements for EPI-DOC (HR, 0.71; 95% CI, 0.53 to 0.95; $P = .02$) compared with EPI × 6 (HR, 0.79; 95% CI, 0.58 to 1.08; $P = .14$). However, only BCFS was statistically significant. This observation is likely due to the larger number of events included in BCFS, including the smaller number of local recurrences in the EPI-DOC group, which are not included in the MFS analysis.

Toxicity

Overall, 791 patients (EPI × 6, n = 388; EPI-DOC, n = 403) of the 794 who received at least one chemotherapy cycle had toxicity information available (Table 4); 773 patients (EPI × 6, n = 377; EPI-DOC, n = 396) received at least cycle 4 of treatment and had toxicity information available. During chemotherapy, 45.5% of patients reported at least one grade 3 or 4 adverse event; 40.2% reported a grade 3 or 4 event between cycles 4 and 6. For cycles 1 to 3 in which all patients received epirubicin, the treatment groups were well balanced in terms of their toxicity profile. When grades 3 or 4 toxicities occurring during cycles 4 to 6 were analyzed, docetaxel appeared more toxic than epirubicin for the prespecified toxicities: febrile neutropenia (epirubicin, n = 2 [0.5%] and docetaxel, n = 34 [8.6%]; $P < .001$), neutropenia (epirubicin, n = 9 [2.4%] and docetaxel, n = 38 [9.6%]; $P < .001$), skin disorders (epirubicin, n = 0 [0.0%] and docetaxel, n = 7 [1.8%]; $P = .002$), and stomatitis (epirubicin, n = 6 [1.6%] and

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Table 4. Number of All-Grade and Grades 3 and 4 Adverse Events by NCI-CTC During Chemotherapy

	All-Grade Toxicities										Grades 3 and 4 Toxicities									
	Cycles 1-3					Cycles 4-6					Cycles 1-3					Cycles 4-6				
	EPI × 6 (n = 388)		EPI-DOC (n = 403)			EPI × 6 (n = 377)		EPI-DOC (n = 396)			EPI × 6 (n = 388)		EPI-DOC (n = 403)			EPI × 6 (n = 377)		EPI-DOC (n = 396)		
Toxicity	No.	%	No.	%	*P*	No.	%	No.	%	*P*	No.	%	No.	%	*P*	No.	%	No.	%	*P*
Prespecified																				
Anemia	85	21.9	89	22.1	1.00	125	33.2	126	31.8	.70	13	3.4	13	3.2	1.00	15	4.0	13	3.3	.70
Febrile neutropenia	10	2.6	9	2.2	.82	7	1.9	51	12.9	< .001	5	1.3	5	1.2	1.00	2	0.5	34	8.6	< .001
Leukopenia	74	19.1	83	20.6	.59	83	22.0	99	25.0	.35	9	2.3	19	4.7	.08	6	1.6	49	12.4	< .001
Neutropenia	53	13.7	51	12.7	.75	54	14.3	54	13.6	.84	9	2.3	14	3.5	.40	9	2.4	38	9.6	< .001
Thrombocytopenia	2	0.5	0	0.0	.24	3	0.8	1	0.3	.36	1	0.3	0	0.0	.49	1	0.3	1	0.3	1.00
Alopecia	350	90.2	357	88.6	.49	343	91.0	348	87.9	.20	66	17.0	82	20.3	.24	73	19.4	91	23.0	.25
Diarrhea	29	7.5	30	7.4	1.00	21	5.6	70	17.7	< .001	0	0.0	3	0.7	.25	1	0.3	10	2.5	.01
Infection	71	18.3	71	17.6	.85	50	13.3	89	22.5	.001	6	1.5	11	2.7	.33	8	2.1	12	3.0	.50
Lethargy	14	3.6	24	6.0	.14	15	4.0	25	6.3	.15	0	0.0	1	0.2	1.00	0	0.0	3	0.8	.25
Musculoskeletal symptoms	17	4.4	12	3.0	.35	12	3.2	30	7.6	.01	0	0.0	0	0.0	—	0	0.0	5	1.3	.06
Myalgia/arthralgia	7	1.8	8	2.0	1.00	7	1.9	81	20.5	< .001	1	0.3	0	0.0	.49	1	0.3	8	2.0	.04
Nausea/vomiting	246	63.4	268	66.5	.37	211	56.0	179	45.2	.003	5	1.3	15	3.7	.04	8	2.1	15	3.8	.21
Peripheral neuropathy	4	1.0	7	1.7	.55	8	2.1	52	13.1	< .001	0	0.0	0	0.0	—	0	0.0	2	0.5	.50
Parethesia	8	2.1	8	2.0	1.00	7	1.9	41	10.4	< .001	0	0.0	0	0.0	—	0	0.0	4	1.0	.12
Neurological, other	51	13.1	51	12.7	.92	35	9.3	67	16.9	.002	2	0.5	3	0.7	1.00	0	0.0	5	1.3	.06
Edema	15	3.9	20	5.0	.49	24	6.4	64	16.2	< .001	0	0.0	1	0.2	1.00	1	0.3	5	1.3	.22
Skin disorders	29	7.5	28	6.9	.79	17	4.5	77	19.4	< .001	2	0.5	0	0.0	.24	0	0.0	7	1.8	.002
Nail abnormalities	9	2.3	22	5.5	.03	26	6.9	107	27.0	< .001	0	0.0	0	0.0	—	0	0.0	5	1.3	.06
Stomatitis	149	38.4	138	34.2	.24	117	31.0	196	49.5	< .001	3	0.8	6	1.5	.51	6	1.6	20	5.1	.009
Thromboembolic events	7	1.8	4	1.0	.38	11	2.9	3	0.8	.03	1	0.3	0	0.0	.49	0	0.0	0	0.0	—
Not prespecified																				
Pyrexia	10	2.6	15	3.7	.36	9	2.4	32	8.1	< .001	1	0.3	2	0.5	1.00	3	0.8	4	1.0	1.00
Eye disorders	19	4.9	8	2.0	.03	4	1.1	21	5.3	.001	1	0.3	0	0.0	.49	0	0.0	0	0.0	—

Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; EPI × 6, six cycles of epirubicin; EPI-DOC, three cycles of epirubicin followed by three cycles of docetaxel.

docetaxel, n = 20 [5.1%]; *P* = .009). These toxicities and several other prespecified adverse events, including diarrhea and neurologic disorders, were all more common at any grade in docetaxel-treated patients during cycles 4 to 6.

The persistent adverse effects of any grade that differed significantly between the chemotherapy arms were peripheral neuropathy (EPI × 6, n = 1 [0.3%] and EPI-DOC, n = 23 [6.2%]; *P* < .001), edema (EPI × 6, n = 8 [2.2%] and EPI-DOC, n = 25 [6.7%]; *P* = .006), and nail abnormality (EPI × 6, n = 1 [0.3%] and EPI-DOC, n = 20 [5.4%]; *P* < .001). The median duration of these adverse effects were 20, 20, and 9 months, respectively.

At baseline, nine patients had abnormal ECGs; all but one patient had chemotherapy as planned, because the clinician concluded that, despite ECG findings, there was no evidence of serious cardiac disease. In addition, 601 patients had LVEF recorded; three had abnormal assessments, of which two did not receive chemotherapy. During follow-up, four patients in the epirubicin arm but none in the EPI-DOC arm developed dyspnea and were diagnosed as having congestive cardiac failure (as defined locally by cardiologist review).

QOL

There was no significant difference in overall QOL between treatments. A comparison of change from baseline (on overall Global Health Status and by individual scales) between randomly assigned groups was performed for patients at 9 months (epirubicin, n = 45; EPI-DOC, n = 61), 2 years (epirubicin, n = 84; EPI-DOC, n = 88), and 5 years (epirubicin, n = 49; EPI-DOC, n = 65; Appendix Table A1, online only). None of the scales showed a statistically significant difference between the randomly assigned groups.

DISCUSSION

The results of this randomized, controlled trial provides evidence that, after three cycles of epirubicin monotherapy, the substitution of docetaxel for epirubicin for the last three cycles of chemotherapy results in improved DFS and OS in postmenopausal patients with breast cancer. The improvement in OS, however, comes at a cost in terms of adverse effects, because patients who switch to docetaxel suffer significantly in terms of febrile neutropenia, skin disorders, and stomatitis, and they have a higher incidence of other chemotherapy-related toxicities. However, this does not impact QOL during the follow-up period. One potential benefit of reducing the anthracycline dose would be to reduce the incidence of cardiac events.[14] Indeed, cardiac failure (n = 4) was restricted to those receiving epirubicin alone.

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Since we began our study, several other groups have reported the results of adjuvant studies of taxanes. These studies have different designs and use different taxanes. Broadly, there are two types of adjuvant taxane trials—those in which the taxane was added to the control regimen,[15-21] and those in which the taxane was substituted for another drug in an established regimen, including trials in which the taxane was sequenced in comparison with another regimen in a similar number of cycles of treatment.[19,22-26] Meta-analyses of these trials, the latest of which was presented as the Taxotere as Adjuvant Chemotherapy (TACT) trial, have shown modest benefits in terms of DFS for taxane-treated patients (DFS combined-effect HR, 0.85; 95% CI, 0.81 to 0.90).[24] Our results represent a slightly larger benefit than that seen overall, and it is noteworthy that DEVA is the only trial with a single-agent control regimen. The difference in OS in our study was most clear after 2 years, similar to the Grupo Español de Investigación en Cáncer de Mama (GEICAM) 9906 study.[22]

Given these uncertain results, trialists have explored clinical and biologic subgroups in the hope of finding a group of patients who would clearly benefit from taxane treatment. As yet, no biomarker or disease subtype has consistently been shown to be predictive of a taxane effect.[24,27]

The optional random assignment of the timing of tamoxifen indicates no evidence for major differences in toxicity or thromboembolic event rates between concurrent or sequential tamoxifen, but there is insufficient power to detect small differences. In summary, DEVA suggests that replacing the final three cycles of epirubicin by docetaxel chemotherapy improves both DFS and OS in postmenopausal patients with node-positive breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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