

Multicycle Dose-Intensive Chemotherapy for Women With High-Risk Primary Breast Cancer: Results of International Breast Cancer Study Group Trial 15-95

International Breast Cancer Study Group

ABSTRACT

Purpose

To compare adjuvant dose-intensive epirubicin and cyclophosphamide chemotherapy administered with filgrastim and progenitor cell support (DI-EC) with standard-dose anthracycline-based chemotherapy (SD-CT) for patients with early-stage breast cancer and a high risk of relapse, defined as stage II disease with 10 or more positive axillary nodes; or an estrogen receptor-negative or stage III tumor with five or more positive axillary nodes.

Patients and Methods

Three hundred forty-four patients were randomized after surgery to receive seven cycles of SD-CT over 22 weeks, or three cycles of DI-EC (epirubicin 200 mg/m² plus cyclophosphamide 4 gm/m² with filgrastim and progenitor cell support) over 6 weeks. All patients were assigned tamoxifen at the completion of chemotherapy. The primary end point was disease-free survival (DFS).

Results

After a median follow-up of 5.8 years (range, 3 to 8.4 years), 188 DFS events had occurred (DI-EC, 86 events; SD-CT, 102 events). The 5-year DFS was 52% for DI-EC and 43% for SD-CT, with hazard ratio of DI-EC compared with SD-CT of 0.77 (95% CI, 0.58 to 1.02; *P* = .07). The 5-year overall survival was 70% for DI-EC and 61% for SD-CT, with a hazard ratio of 0.79 (95% CI, 0.56 to 1.11; *P* = .17). There were eight cases (5%) of anthracycline-induced cardiomyopathy (two fatal) among those who received DI-EC. Women with hormone receptor-positive tumors benefited significantly from DI-EC.

Conclusion

There was a trend in favor of DI-EC with respect to disease-free survival. A larger trial or meta-analysis will be required to reveal the true effect of dose-intensive therapy.

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INTRODUCTION

Women with breast cancer and 10 or more involved axillary nodes have a 5-year relapse rate of 70% to 80% without treatment.¹ Even in published results of the best standard adjuvant chemotherapy for this group, at least half relapse and one third are dead within 5 years of diagnosis,^{2,3} while within 10 years, 70% have relapsed, and 60% are dead.⁴ A poor prognosis is also associated with large tumors and those that are estrogen receptor (ER)-negative.^{5,6} Long-term survival is also poor in women with locally advanced (T3 tumors) breast cancer.⁷⁻⁹

One approach to improving the management of these women has been to administer dose-intensive adjuvant treatment by either increasing the total dose of chemotherapy, reducing the interval between cycles or a combination of these approaches. A widely researched method is

to deliver a single course of myeloablative treatment with progenitor cell support as consolidation after multiple initial cycles of conventional dose chemotherapy. The basis of this strategy is to initially reduce tumor load followed by a "mopping up" procedure for the remaining, presumably resistant cells. A contrasting tactic has been to administer dose-intensive chemotherapy from the start of treatment based on the hypothesis that this might give the best chance of killing relatively resistant cancer cells.

We developed a regimen of upfront, multi-cycle, dose-intensive epirubicin and cyclophosphamide (DI-EC), and previously reported on the safety and feasibility of this approach¹⁰ and 5-year follow-up in a single-arm study of 99 women with early-stage breast cancer.¹¹ We now report the results of International Breast Cancer Study Group (IBCSG) Trial 15-95, which compared DI-EC with

From the International Breast Cancer Study Group. Appendix lists the names and affiliations of the writing committee, and participants and authors of Trial 15-95.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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conventional adjuvant chemotherapy in women with poor-prognosis breast cancer.

PATIENTS AND METHODS

Trial Design

IBCSG Trial 15-95 was designed to compare conventional with DI-EC adjuvant chemotherapy for women at high risk for recurrence (Fig 1). Between July 1995 and March 2000, 344 women with operable breast cancer from centers in Europe, Australia, and Asia were enrolled onto the study. Patients were randomly assigned within 6 weeks of surgery, and all patients were assigned to receive tamoxifen 20 mg/d for 5 years once chemotherapy had finished. Radiotherapy was mandatory after breast-conserving therapy and recommended for all other patients, and was given after completion of DI-EC. For the SD-CT group, it was either integrated with the chemotherapy or given after completion of chemotherapy, according to institutional guidelines. Randomized treatment was to commence within 10 weeks of surgery.

Standard chemotherapy consisted of intravenous injections of doxorubicin 60 mg/m² or epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² (AC or EC, respectively) every 3 weeks for four cycles. This was immediately followed by oral cyclophosphamide 100 mg/m² daily for 14 days, and intravenous injections of methotrexate 40 mg/m² and fluorouracil 600 mg/m² on days 1 and 8 ("classical" CMF), every 4 weeks for three cycles (described hereafter SD-CT).

For patients randomized to receive DI-EC, peripheral-blood progenitor cells were collected before chemotherapy. Filgrastim 10 µg/kg was given subcutaneously daily for 6 days with leukapheresis on days 5, 6, and 7 of administration. Chemotherapy consisted of epirubicin 200 mg/m² intravenously over 1 hour on day 1 and cyclophosphamide 4 gm/m² on day 2, given as 1 gm/m² intravenously over 30 minutes in four divided doses. Further details of supportive care are described elsewhere.^{26,27} DI-EC was given every 3 weeks for three cycles. Dose modifications were not allowed, but treatment could be delayed until adequate recovery from toxicity in previous cycles (Eastern Cooperative Oncology Group [ECOG] performance status ≤ 2; absolute neutrophil count ≥ 1.5 × 10⁹/L; platelet count ≥ 100 × 10⁹/L; recovery from grade 3-4 nonhematologic toxicities).

Informed consent was obtained from all patients, and the institutional review committee at each participating center approved the study. The IBCSG conducted an extensive audit of 100% of cases that included source data verification of all eligibility criteria as well as event reporting. Randomization was conducted centrally (at the coordinating centers in Bern, Switzerland, and Sydney, Australia). A permuted blocks randomization schedule was produced by use of pseudorandom numbers generated by a congruence method.

Patient Population

A patient was considered "high risk" if she was younger than 66 years and her breast cancer met one of the following categories: (1) had 10 or more involved axillary nodes and was ER-positive; (2) had five or more involved axillary nodes and was ER-negative; and (3) had five or more involved axillary

nodes and operable T3 tumor. Before random assignment, all patients had undergone modified radical mastectomy or lumpectomy and axillary node dissection. The main eligibility criteria were ECOG performance status score of 0 to 2; normal hematologic, hepatic, and renal function; no evidence of distant disease on chest x-ray, bone scan, and liver imaging (computed tomography scan or ultrasound); and normal cardiac function as assessed by radionuclide scan or echocardiogram. Women were excluded if they had locally advanced breast cancer (primary tumor fixed to chest wall, satellite skin nodules, involved supraclavicular nodes, inoperable matted axillary nodes), bilateral breast cancer, prior treatment for breast cancer, history of previous cancer (except basal cell carcinoma or in situ cancer of the cervix), serious underlying medical or psychiatric condition, or were pregnant. Although all patients enrolled were included in this intent-to-treat analysis, eight patients were found to be ineligible for the following reasons: pT4 primary tumors (three patients), inadequate staging procedures (one patient), metastatic disease (one patient), concurrent malignancy (one patient), incompletely resected cancer on histology (one patient), and brachytherapy before random assignment (one patient).

A woman was regarded as post menopausal if she (1) had her last normal menstrual period more than 6 months before random assignment (and was not receiving hormone-replacement therapy [HRT] and never had a hysterectomy), (2) had a hysterectomy, was not receiving HRT, and was older than 55 years (or ≤ 55 years with postmenopausal luteinizing hormone, follicle-stimulating hormone, and estradiol levels), (3) was receiving HRT and was ≥ 50 years or had no menstruation within 6 months before starting HRT.

Grade determination was based on the local Bloom-Richardson (BR) scoring, if available. If the BR scoring was not available from the participating center, then grade was based the local 3-point differentiation scale. If neither the local BR, nor the local differentiation scale was available, then grade was based on the central review BR scoring. Cancers were classified as ER-negative based on immunohistochemistry (IHC) quantitative result of less than 1% stained cells, IHC qualitative assay result of "negative" or "borderline," or biochemical assay of less than 10 fmol/mg of cytosol protein. In most cases (88%), ER status was evaluated with IHC.

Patients were evaluated at the beginning of each course of chemotherapy and at the beginning and end of radiotherapy (if delivered). Patients underwent clinical, hematologic and biochemical assessment every 3 months for 2 years, then every 6 months for the next 3 years, then yearly thereafter. Chest x-ray was performed every 6 months for 5 years, and then yearly, and mammography was performed yearly.

Statistical Considerations

Disease-free survival (DFS) was defined as the length of time from the date of randomization to any recurrent breast cancer (including ipsilateral and contralateral breast recurrence), the appearance of a second (nonbreast) primary malignancy, or death, whichever occurred first. Overall survival (OS) was defined as the length of time from the date of randomization to death from any cause.

DFS and OS percentages, SEs, and treatment effect comparisons were obtained from the Kaplan-Meier method,¹² Greenwood's formula,¹³ and log-rank tests,¹⁴ respectively. Cox proportional hazards regression models¹⁵ were

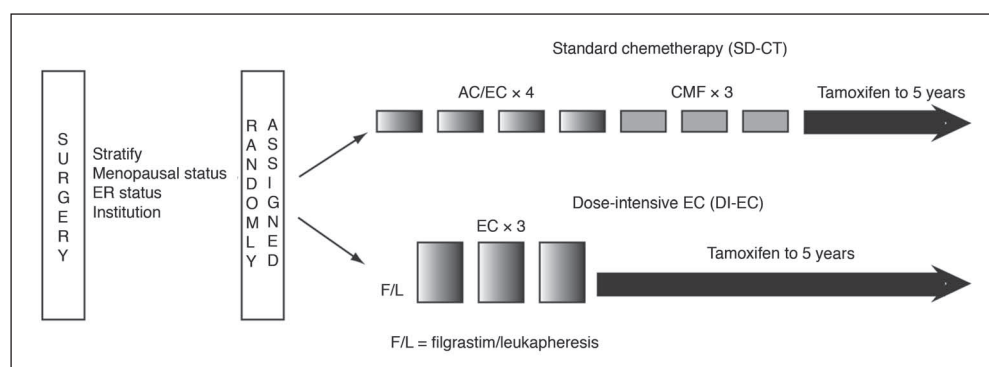


Fig 1. International Breast Cancer Study Group trial 15-95 schema. Three hundred forty-four patients were randomized to receive either standard chemotherapy (AC or EC × 4 followed by CMF × 3) or dose-intensive EC × 3. All patients were assigned tamoxifen. DI-EC, dose-intensive doxorubicin and cyclophosphamide.

used to control for prognostic features, to estimate hazard ratios (HRs) and 95% CIs for the treatment comparisons, and to test for interactions between potential predictive factors and treatment effects.

The intention to perform separate analyses according to ER status was specified in the protocol. The trial was originally designed to accrue 210 patients to detect an improvement in median survival from 4 to 7.25 years and was amended to 300 patients in September 1997 to provide 80% power (using a two-sided .05 log-rank test), to detect an improvement in median survival from 4 to 6.5 years using DI-EC (equivalent to an improvement in 5-year survival from 42% to 58.5%, or an HR of 0.62 comparing DI-EC with SD-CT). The study was powered to detect a large difference in survival in order to justify the greater expected toxicity of DI-EC. The target number of deaths was 135. The Data and Safety Monitoring Committee reviewed accrual and safety twice a year. Study continuation was recommended at two predetermined interim efficacy analyses performed in January 1999 and June 2000.

RESULTS

Patient, Tumor, and Local Treatment Characteristics

Patient, tumor, and local treatment characteristics of the 344 enrolled patients are presented in Table 1. The women were aged between 25 and 65 years. Mastectomy was the primary surgery in 69% of women while breast-conserving surgery was performed in 31%. Radiotherapy was administered to 40% of the former group and 95%

of the latter group. There was no difference in the surgical approach or the proportion of women receiving radiotherapy between the treatment groups.

Adjuvant Treatment

Of the 171 patients randomized to SD-CT, 64% received epirubicin and 36% received doxorubicin. The two regimens had similar numbers of patients completing the assigned treatment (92% SD-CT and 87% DI-EC; Table 2). For women given SD-CT and for those given DI-EC, the median time from surgery to commencement of chemotherapy was 30 days and 46 days, respectively, and the median duration over which chemotherapy was given was 155 days and 50 days, respectively. Delays in administration of the second and third cycles of DI-EC beyond the planned 3-week interval occurred in 49% of the cycles, mostly due to logistical reasons or unresolved toxicity. Tamoxifen was given to 95% of the women with ER-positive tumors and 87% of women with ER-negative tumors.

Adverse Effects

Table 2 presents the grade 3 and 4 toxicities reported during chemotherapy. Toxicities in the SD-CT group were as expected, and there were no drug-related deaths in the SD-CT group. In the DI-EC group, treatment-related toxicities were similar to those previously reported in a pilot study of this regimen.¹¹ Nearly all patients on

Table 1. Patient, Tumor, and Local Treatment Characteristics

	SD-CT (EC/AC × 4 → CMF × 3)		DI-EC (EC × 3)		Total	
	No.	%	No.	%	No.	%
Total cases	171		173		344	
Estrogen receptor status						
Negative	96	56	91	52	187	54
Positive	73	43	81	47	154	45
Unknown	2	1	1	1	3	1
Age, years						
< 40	39	23	44	25	83	24
40-59	123	72	125	73	248	72
≥ 60	9	5	4	2	13	4
Menopausal status						
Premenopausal	115	67	117	67	232	67
Postmenopausal	56	33	56	33	112	33
Treatment						
Mastectomy no RT	64	37	78	45	142	41
Mastectomy + RT	48	28	47	27	95	28
Breast conservation no RT	2	1	3	2	5	1
Breast conservation + RT	57	34	45	26	102	30
No. of positive nodes						
5-9	37	22	54	31	91	26
≥ 10	134	78	119	69	253	74
Tumor size, cm*						
< 2	45	26	59	34	104	30
2-5	91	54	84	49	175	51
> 5	33	19	30	17	63	18
Tumor grade†						
1	5	3	12	7	17	5
2	59	35	64	37	123	36
3	106	62	95	56	201	59

Abbreviations: SD-CT, standard-dose chemotherapy; EC/AC, epirubicin 90 mg/m² or doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m² every 3 weeks; CMF, oral cyclophosphamide 100 mg/m² daily for 14 days and intravenous injections of methotrexate 40 mg/m² and fluorouracil 600 mg/m² days 1 and 8 every 4 weeks; DI-EC, dose-intensive epirubicin 200 mg/m² day 1 and cyclophosphamide 4 g/m² day 2 every 3 weeks with filgrastim and progenitor cell support; RT, radiotherapy.

*Tumor size unknown in two patients; RT, radiotherapy.

†Histologic grade unknown in three patients.

Table 2. Treatment Compliance and Adverse Events

	SD-CT (EC/AC × 4 → CMF × 3)		DI-EC (EC × 3)	
	Grade 3	Grade 4	Grade 3	Grade 4
Randomized	171		173	
Started assigned chemotherapy*				
No.	165		159	
%	96		92	
Completed assigned chemotherapy†				
No.	157		150	
%	92		87	
Toxicity, % of patients				
Neutropenia	41	43	0	100
Thrombocytopenia	0	0	2	97
Anemia	4	0	70	10
Sepsis	4	0	14	4
Stomatitis/mucositis	1	0	26	0
Nausea/vomiting	7	—	13	—
Diarrhea	1	0	2	0
Headache	2	—	2	—
DVT/PE	0	1	1	0
Hepatotoxicity	0	0	3	0
Cystitis	0	0	2	0

NOTE. Dash indicates grade not defined.

Abbreviations: SD-CT, standard-dose chemotherapy; EC/AC, epirubicin 90 mg/m² or doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m² every 3 weeks; CMF, oral cyclophosphamide 100 mg/m² daily for 14 days and intravenous injections of methotrexate 40 mg/m² and fluorouracil 600 mg/m² days 1 and 8 every 4 weeks; DI-EC, dose-intensive epirubicin 200 mg/m² day 1 and cyclophosphamide 4 g/m² day 2 every 3 weeks with filgrastim and progenitor cell support; DVT/PE, deep venous thrombosis/pulmonary embolism.

*Reasons for not SD-CT: given DI-EC (four patients), non-protocol regimen (1), unknown (1); reasons for not starting DI-EC: given SD-CT (4), non-protocol regimen (5), early recurrence (3), refusal (2).

†Reasons for not completing SD-CT: received 1 cycle AC/EC and switched hospital (2 patients), recurrence after AC/EC completed (1), stopped during CMF (5); reasons for not completing DI-EC: toxicity (5), refusal (1), switched to non-protocol treatment (3).

DI-EC experienced grade 4 neutropenia and thrombocytopenia, while anemia occurred in 80% of patients. Hospitalization after cycle 1 occurred in all patients who received DI-EC (median days hospitalized, 15; range, 3 to 25 days).

There were four (2.5%) treatment-related deaths: two women who received DI-EC died during chemotherapy, one from sepsis due to severe neutropenia with no evidence of recurrence, the other from respiratory failure (with evidence of liver metastases at autopsy); two additional patients died from anthracycline-induced cardiomyopathy 20 and 10 months after completion of chemotherapy, one of whom had a local recurrence treated with radiotherapy, while the other died before a cancer event. Five additional patients developed evidence of grade 3 or 4 cardiac failure within 1 to 12 months of chemotherapy, and a sixth patient developed grade 3 cardiac failure 42 months after chemotherapy, for a total of eight patients (5%) reporting grade 3 to 5 cardiac events. One patient on SD-CT and one on DI-EC died from unrelated causes without evidence of recurrence 32 and 41 months after random assignment, respectively.

There were five cases of second (nonbreast) malignancies occurring without evidence of recurrence of breast cancer, as follows: SD-CT: melanoma 22 months after study entry; DI-EC: melanoma (30 months), endometrial cancer (34 months; patient received 30 months of tamoxifen), ovarian cancer (37 months), and head and neck cancer (74 months). One patient given DI-EC was diagnosed with acute myelogenous leukemia concurrently with local breast cancer recurrence (20 months). The second malignancies were included as DFS events at the time of diagnosis.

Chemotherapy-Induced Amenorrhea

Menstrual status during and after treatment was available for 193 of the 232 women who were premenopausal at the time of random assignment. Amenorrhea, defined as no menses reported during months 7, 8, and 9 from random assignment, was more common on DI-EC than on SD-CT (93% v 78%), and was also more often permanent (81% v 63%). This difference was especially marked in women younger than 40 years, for whom amenorrhea occurred for DI-EC and SD-CT in 85% and 48%, and was permanent for 61% and 24%, respectively.

DFS and OS

Patients on SD-CT had a lower rate of relapse than anticipated, so the power to detect a difference in survival was less than originally planned. The current analysis was evaluated after 188 DFS events had occurred (102 on SD-CT and 86 on DI-EC), at a median follow-up of 5.8 years (range, 3 to 8.4 years). The 5-year DFS was 43% and 52%,

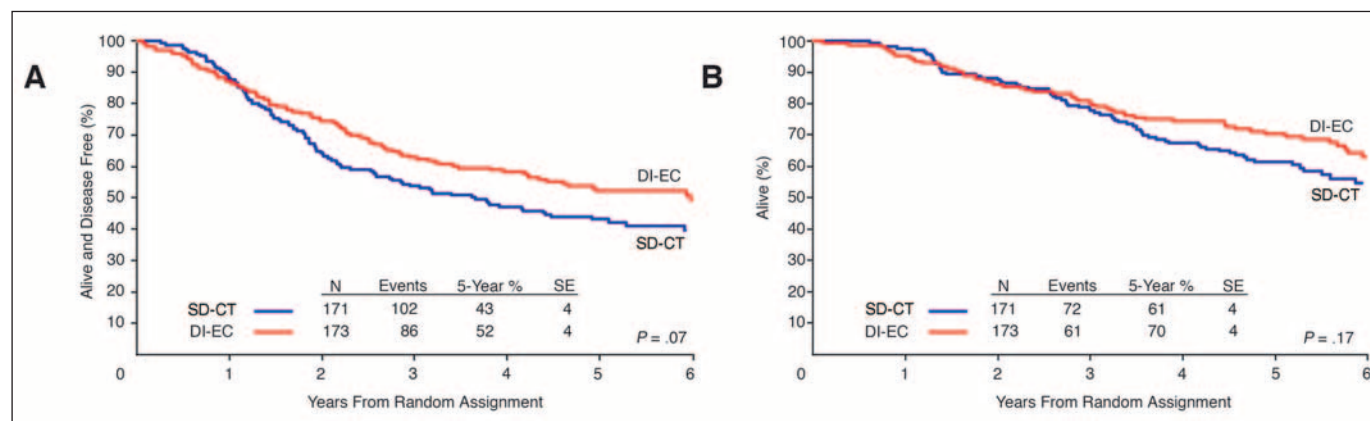


Fig 2. Disease-free survival (panel A) and overall survival (panel B) comparing patients assigned to dose-intensive EC × 3 (DI-EC, red line) with patients assigned to standard chemotherapy (SD-CT, blue line). The median follow-up was 5.8 years.

respectively, with an HR of 0.77 (95% CI, 0.58 to 1.02; $P = .07$) in favor of DI-EC (Fig 2A). Similarly, there was a nonsignificant trend favoring DI-EC in overall survival. There were 72 deaths on SD-CT and 61 on DI-EC. The 5-year OS was 61% and 70%, respectively, with an HR of 0.79 (95% CI, 0.56 to 1.11; $P = .17$) in favor of DI-EC (Fig 2B).

Cox proportional hazard models were used to estimate the treatment effect after adjustment for the following baseline characteristics: age, menopausal status, type of local surgery, hormone receptor status, tumor size, number of involved axillary nodes, and tumor grade. After adjusting, there remained a trend in favor of DI-EC, with a DFS HR of 0.81 (95% CI, 0.61 to 1.10, $P = .17$) and an OS HR of 0.87 (95% CI, 0.61 to 1.24), $P = .45$.

Differences in the magnitude of DI-EC treatment effect according to baseline characteristics were examined (Fig 3); interactions were

not statistically significant. Subgroups having the greatest observed DI-EC effect include patients with ER-positive breast cancer (DFS HR, 0.58; 95% CI, 0.36, 0.94; $P = .02$; OS HR, 0.53; 95% CI, 0.28 to 1.00; $P = .05$), and those with primary tumors 2 to 5 cm (DFS HR, 0.51; 95% CI, 0.34 to 0.78; $P < .01$; and OS HR, 0.65; 95% CI, 0.39 to 1.06; $P = .08$).

The sites of first failure are shown in Table 3. Local failure as the site of first recurrence occurred in 5.2% of all patients and was similar between treatment groups. The DI-EC regimen seemed to control distant recurrence better than SD-CT, especially in the bone. Two supplemental analyses were performed, both motivated by observed imbalances between the treatment groups. The first excluded patients who did not receive any of their prescribed chemotherapy (six in the SD-CT group and 14 in the DI-EC group). This analysis of DFS

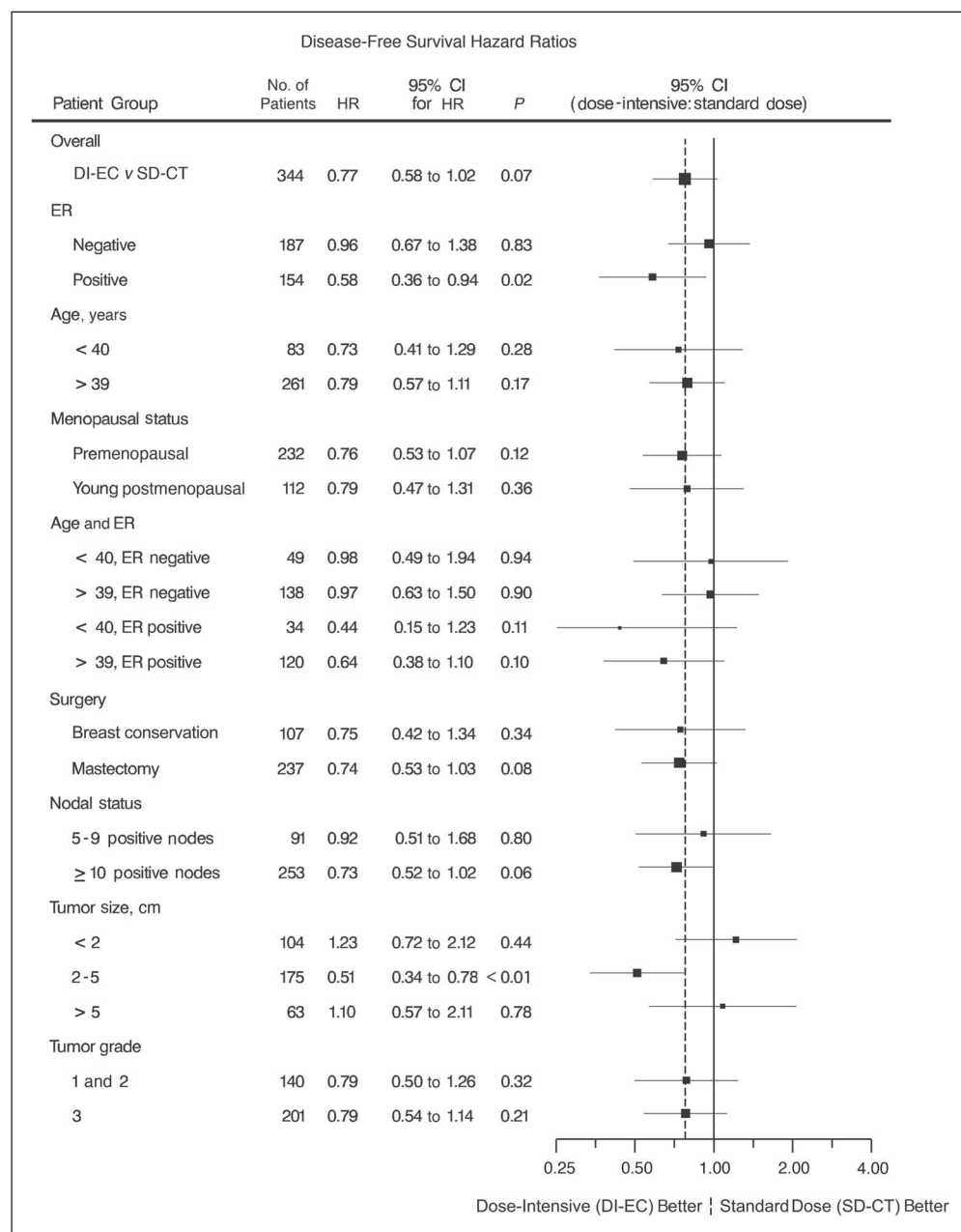


Fig 3. Disease-free survival hazard ratios (DI-EC:SD-CT) and 95% CIs for recurrence. The size of the squares corresponds to the amount of statistical information. Confidence intervals to the left of the vertical line indicate subgroups for which DI-EC may be beneficial with respect to disease-free survival. All analyses for interaction were unplanned, except within ER status. Pts, patients; HR, hazard ratio; CI, confidence interval; DI-EC, dose-intensive epirubicin-cyclophosphamide; SD-CT, standard-dose chemotherapy; ER, estrogen receptor.

Table 3. Sites of First Failure

Sites of failure	SD-CT (EC/AC × 4 → CMF × 3; n = 171)		DI-EC (EC × 3; n = 173)		Total (n = 344)	
	No.	%	No.	%	No.	%
Local	8	4.7	10	5.8	18	5.2
Contralateral ± local	2	1.2	3	1.7	5	1.5
Regional ± above	10	5.8	6	3.5	16	4.7
Distant ± above	80	46.8	58	33.5	138	40.1
Soft tissue ± above	5	2.9	7	4.0	12	3.5
Bone ± above	28	16.4	12	6.9	40	11.6
Viscera ± above	47	27.5	39	22.5	86	25.0
Second (nonbreast) malignancy*	1	0.6	4	2.3	5	1.4
Death without prior cancer event	1	0.6	4	2.3	5	1.4
Unknown	0	0.0	1	0.5	1	0.3
Total failures	102	59.6	86	49.7	188	54.7
Total deaths from any cause	72	42.1	61	35.3	133	38.7

Abbreviations: SD/CT, standard-dose chemotherapy; EC/AC, epirubicin 90 mg/m² or doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m² every 3 weeks; CMF, oral cyclophosphamide 100 mg/m² daily for 14 days and intravenous injection of methotrexate 40 mg/m² and fluorouracil 600 mg/m² days 1 and 8 every 4 weeks; DI-EC, dose-intensive epirubicin 200 mg/m² day 1 and cyclophosphamide 4 g/m² day 2 every 3 weeks with filgrastim and progenitor cell support.

*One additional patient had a second malignancy concurrent with local breast recurrence.

showed a nonsignificant trend favoring DI-EC with an HR of 0.78 (95% CI, 0.58 to 1.05; $P = .11$). The second included all patients, but redefined DFS to censor nonbreast malignancies (one SD-CT and four DI-EC). This analysis resulted in a significant difference favoring DI-EC, with an HR of 0.73 (95% CI, 0.55 to 0.98; $P = .04$).

DISCUSSION

Evidence of the benefit associated with high-dose chemotherapy (HDC; single myeloablative course with progenitor cell support after multiple initial cycles of conventional dose chemotherapy) to women with poor-prognosis breast cancer was first suggested in small, uncontrolled studies and registry data that showed prolongation of disease-free and overall survival compared with historical controls. Conflicting evidence of benefit has come from small randomized trials^{16,17} and early data from larger trials.¹⁸⁻²⁴ However, some degree of clarification has emerged from the recent publication of more complete data from larger randomized trials. Tallman et al showed no benefit from consolidation HDC after induction conventional-dose treatment in women with primary breast cancer and 10 or more involved axillary nodes.² Rodenhuis et al²⁵ and Leonard et al²⁶ found no improvement in OS or DFS for a similar approach in women with four or more involved axillary nodes. Zander et al²⁷ observed a nonsignificant trend in favor of HDC with respect to DFS but not overall survival in women with 10 or more nodes, while Peters et al²⁸ found no improvement in DFS or OS following HDC in a similar population.

Improvements in outcome have been demonstrated with delivery of increased total dose and dose-intensity of chemotherapy within a range not requiring support with growth factors or progenitor cells.²⁹⁻³¹ Citron et al showed that reducing the interval between cycles (increasing *dose density*) with the aid of filgrastim also resulted in significantly increased survival in women with node-positive breast cancer.³

The evaluation of a dose-intensive regimen, such as in IBCSG 15-95, must weigh the potential advantage in efficacy and shorter

chemotherapy duration against the expected increase in toxicity and the costs of treatment administration. IBCSG Trial 15-95 compared a conventional dose anthracycline-based regimen given over 22 weeks and multicycle dose-intensive anthracycline-based chemotherapy administered over 6 weeks. There was a 23% reduction in the risk of a DFS event and a 21% reduction in the risk of death in patients treated with DI-EC; although, even after almost 6 years of follow-up, these differences did not reach statistical significance.

While the acute toxicities of DI-EC were obviously much more severe than those of SD-CT, patients generally recovered to normal health at completion of treatment. The observed acute mortality rate for DI-EC (1%) is similar to other dose-intensive therapies.^{3,25-27} The incidence of severe myelosuppression, the use of antibiotics and blood products, the nature and frequency of severe nonhematologic toxicity, and the rate of long-term effects were almost identical to the previous experience.^{11,32} The trial was conducted in 17 centers from five countries, and it seems that the DI-EC regimen can be safely delivered in a wide range of clinical settings.

The study is quite mature, with a median follow-up of 5.8 years, and a minimum follow-up of 3 years. The relapse rate following SD-CT was lower than expected, which might be partly due to careful selection of patients because of more extensive staging procedures than conducted in many adjuvant studies.³³ Our definition of DFS includes second (nonbreast) malignancies, which were more often observed in the DI-EC arm. If these events were censored, the treatment difference becomes statistically significant. In addition, the design of the study was ambitious in aiming for an HR for OS of 0.62. We conclude that the observed trends in improved DFS and OS favoring DI-EC suggest that dose-intensive treatment may be superior to the conventional approach for high-risk patients. A larger study or meta-analysis of trials with similar designs is required to determine the benefit of DI-EC as delivered in this study.

The adjuvant therapy used in this study was considered optimal at the time the trial was designed. Radiotherapy was required for all patients who had less than mastectomy, but was optional for

those who had a mastectomy. Although during the course of the trial reports emerged of the benefit of radiotherapy after mastectomy for node-positive breast cancer, we decided to leave radiotherapy administration as the choice of the participating center, and in fact, the rate of local recurrence in our trial was much lower than that reported in the radiotherapy studies^{34,35} and similar to contemporary trials of adjuvant therapy in poor-prognosis breast cancer.³ The trial included tamoxifen through 5 years from randomization for both treatment groups. Before the start of the study, the breast cancer overviews³⁶ suggested that tamoxifen may have a small but potentially clinically important effect in receptor-negative disease, a conclusion that has been refuted in subsequent analyses.³⁷ After the publication of the latter paper, we no longer required tamoxifen for the ER- and progesterone receptor-negative cohort.

The subgroup analyses presented in Figure 3 should be interpreted cautiously and are presented to develop hypotheses that require further investigation. Subgroups with the largest estimated DI-EC effect were patients with ER-positive tumors (42% estimated reduction in DFS events) and those with tumors measuring 2 to 5 cm (49% estimated reduction in DFS events). Interaction tests were not statistically significant indicating that these observed differences could represent chance findings. The observations according to ER status and age deserve further study. For example, there could be a true superiority of the DI-EC regimen over standard chemotherapy in the ER-negative cohort,³⁸ which did not emerge in this trial due to the use of

tamoxifen following chemotherapy. Evidence that tamoxifen was associated with a worse outcome in ER-negative subgroups has been reported in adjuvant trials^{39,40} and in trials in which tamoxifen was used for breast cancer prevention.⁴¹ The advantage for DI-EC in the ER-positive cohort might be partially due to differential endocrine effects between the two regimens. In younger premenopausal women (< 40 years old), DI-EC was more likely to induce amenorrhea—an effect that could contribute to improved disease control in patients with ER-positive tumors. Improved results were also observed for older women with ER-positive disease, which suggests that ovarian ablation cannot be the entire explanation, and some alternative endocrine-mediated treatment effect might influence outcome for this cohort.⁴²

There are an increasing number of effective cytotoxic, hormonal, and biologic agents for women with breast cancer and much research is ongoing to determine how best to use these various therapeutic options. The hypothesis that dose-intensity is an important determinant of the efficacy of adjuvant chemotherapy is now supported by the results of a number of trials within the standard dose range and, more recently, at higher doses of chemotherapy administered with the support of growth factors. However, some dose-intensive approaches, such as increasing dose-density, seem to be more effective than others. Our data show that dose-intensive anthracycline-based chemotherapy with progenitor cell support delivered over a short period of time may benefit women with poor-prognosis breast cancer.

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