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ORIGINAL REPORT

Intense Dose-Dense Sequential Chemotherapy With Epirubicin, Paclitaxel, and Cyclophosphamide Compared With Conventionally Scheduled Chemotherapy in High-Risk Primary Breast Cancer: Mature Results of an AGO Phase III Study

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ABSTRACT

Purpose
Patients with primary breast cancer who have extensive axillary lymph node involvement have a poor prognosis after conventional adjuvant therapy. We compared intense dose-dense (IDD) adjuvant chemotherapy with conventionally scheduled adjuvant chemotherapy in patients with high-risk primary breast cancer.

Patients and Methods
In this randomized, phase III trial, a total of 1,284 eligible patients with four or more involved axillary lymph nodes were randomly assigned to receive IDD sequential epirubicin, paclitaxel, and cyclophosphamide (IDD-ETC) every 2 weeks or conventionally scheduled epirubicin/cyclophosphamide followed by paclitaxel every three weeks. The primary end point was event-free survival (EFS).

Results
At a median follow-up of 62 months, 5-year event-free survival rates were 62% in the conventional arm and 70% in the IDD-ETC arm, representing a 28% reduction of the relative risk of relapse ($P < .001$). This benefit was independent of menopausal, hormone receptor, or human epidermal growth factor receptor 2 status. The 5-year overall survival rates were 77% versus 82%, representing a 24% reduction of the relative risk of death ($P = .0285$). IDD therapy was associated with significantly more nonhematologic and hematologic toxicities, but no treatment-related death occurred. Four occurrences of acute myeloid leukemia or myelodysplastic syndrome (MDS) were observed in the IDD-ETC arm. No severe congestive heart failure was reported.

Conclusion
IDD-ETC was less well tolerated compared with conventional chemotherapy but significantly improved event-free and overall survivals in patients with high-risk primary breast cancer who had four or more positive axillary lymph nodes.

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INTRODUCTION

Adjuvant chemotherapy for women with breast cancer has undergone major changes. Today, established adjuvant regimens represent well-defined, different levels of therapeutic potency. Triple-drug or four-drug anthracycline-containing regimens—such as fluorouracil (FU), doxorubicin/epirubicin, and cyclophosphamide; or epirubicin followed by cyclophosphamide, methotrexate, and FU—have shown superiority in comparison to cyclophosphamide, methotrexate, and FU.[1,2] Incorporating taxanes into anthracycline-based schedules yielded, in most studies, an additional benefit in both disease-free survival (DFS) and overall survival (OS),[3-7] and dose-dense anthracycline-based and paclitaxel-based regimens have shown to be more effective than the conventional dosing schedule.[8,9]

The importance of dose-intensity for adjuvant chemotherapy in patients with breast cancer has first described by Hryniuk et al.[10] Higher dose-intensity can be achieved by either increasing the single dose

per cycle (ie, higher dose) or by reducing the intervals between cycles (ie, dose density).[11] The concept called log-cell kill postulated that a given dose of an antineoplastic compound would always kill a certain fraction of the tumor, regardless of the number of cells present.[12] On the basis of that model, higher doses are supposed to be effective because the fraction of destroyed cancer cells will increase with intensification of the dose.

However, the impact of therapy is not only associated with the tumor-cell kill by each dose but also with the rate of cancer regrowth between cycles. Gompertzian kinetics suggest that micrometastases in the adjuvant setting grow faster than established macrometastases; thus, there is likely a higher regrowth of micrometastases between the cycles. Therefore, it has been hypothesized that the administration of cytotoxic drugs with a shortened interval between treatment would be an even more effective strategy for minimizing residual tumor burden than pure dose escalation.[11]

The intense dose-dense (IDD) epirubicin, paclitaxel, and cyclophosphamide (ETC) regimen used in this study encompasses the concepts of dose density, higher dose per cycle, and sequential therapy. Epirubicin, paclitaxel, and cyclophosphamide were chosen on the basis of their high single-agent activities and previous findings, which showed that high dosages of anthracycline-based and taxane-based regimens could be administered safely in a dose-dense manner and with promising results.[13] Initial results of the IDD-ETC trial have been reported in abstract form.[14,15] This article is the first complete reporting.

PATIENTS AND METHODS

Patients

Women with histologically confirmed primary breast cancer of stages II to IIIA with four or more positive axillary lymph nodes were eligible. Additional eligibility criteria included age between 18 and 65 years; M0 status (ie, normal findings on chest radiography, liver ultrasonography, and bone scan); R0 resection of the primary tumor and axilla with a minimum of 10 axillary nodes removed; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; normal left ventricular ejection fraction; neutrophils $\geq$ 1,500/μL; platelets $\geq$ 100, 000/μL; serum creatinine, transaminases, and total bilirubin less than 1.25; and alkaline phosphatase less than 3.0 times the institutional upper normal limit. Major exclusion criteria included a history of severe cardiac disease, previous systemic tumor therapy, and simultaneous contralateral breast cancer or any other cancer except for basal cell skin carcinoma.

Treatment

IDD treatment consisted of sequential administration of epirubicin (150 mg/m^2 intravenously [IV] as bolus infusion) every 2 weeks for three cycles followed by paclitaxel (225 mg/m^2 IV as a 3-hour infusion) every 2 weeks for three cycles followed by cyclophosphamide (2,500 mg/m^2 IV as a 2-hour infusion) every 2 weeks for three cycles. By definition, the ETC regimen was dose dense and used a higher total dose per cycle. Patients received filgrastim subcutaneously (5 μg/kg body weight per day) from days 3 to 10 of each cycle. Women in the IDD-ETC arm were additionally randomly assigned to receive epoetin alfa (150 IU/kg three times weekly) during the whole chemotherapy period or no recombinant human erythropoietin. The standard treatment consisted of four cycles of epirubicin/cyclophosphamide (90/600 mg/m^2 IV on day 1) followed by four cycles of paclitaxel (175 mg/m^2) as a 3-hour infusion (EC$\rightarrow$T). All cycles were administered in 3-week intervals without growth factor support (Fig 2).

Radiation of the supraclavicular, infraclavicular, and parasternal lymph nodes, as well as radiation of the breast in patients with partial mastectomy or to the chest wall in case of mastectomy, was recommended in all patients. Patients with hormone receptor–positive tumors received tamoxifen 20 mg/d for 5 years starting after completion of chemotherapy. After 5 years of tamoxifen treatment, because of the results of the National Cancer Institute of Canada Clinical Trials Group MA. 17 trial[16] in postmenopausal patients, extended adjuvant therapy with letrozole for an additional 5 years was recommended. Left ventricular ejection fraction was measured by echocardiography at baseline, after three cycles of epirubicin, at the end of chemotherapy, and at yearly intervals during follow-up. Complete blood counts were obtained weekly during chemotherapy.

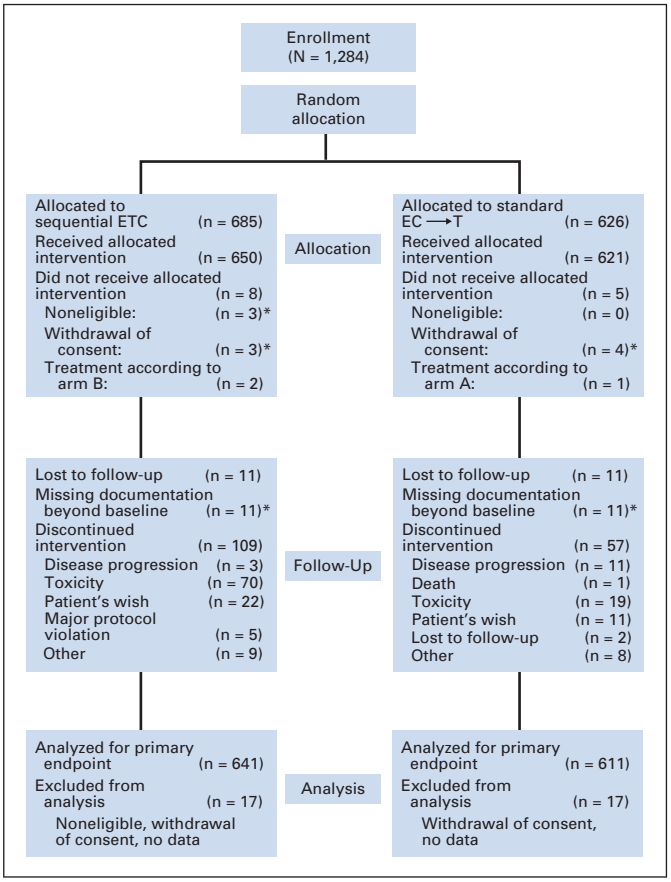

Fig 1. CONSORT trial flow diagram. (*) Excluded from analysis of primary end point. ETC, epirubicin, paclitaxel, and cyclophosphamide; EC$\rightarrow$T, epirubicin and cyclophosphamide followed by paclitaxel.

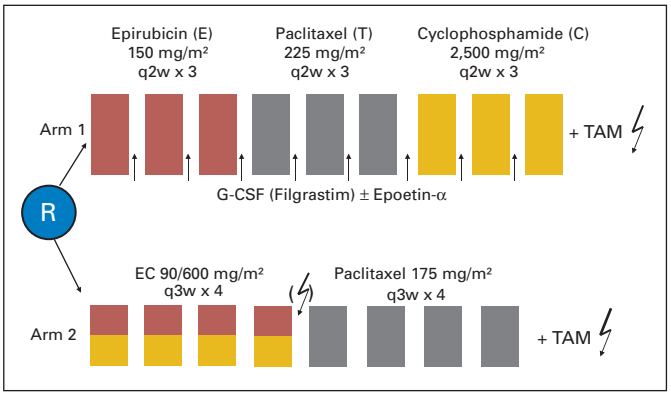

Fig 2. Trial design. q2w, every 2 weeks; G-CSF, granulocyte colony-stimulating factor; TAM, tamoxifen; EC, epirubicin and cyclophosphamide; q3w, every 3 weeks.

Statistical Aspects

At each participating institution, the study was approved by the local institutional review board. Patients were stratified according to institution, menopausal status, and number of lymph nodes involved (four to nine $v \geq 10$).

The study had two primary end points: event-free survival (EFS), with an event defined as locoregional or distant relapse, contralateral breast cancer, second primary cancer occurrence, or death for any reason; and the influence of epoetin alfa on the number of red blood cells for transfusion and the median hemoglobin value. Secondary end points included OS, toxicity, and quality of life.

Overall, 1,154 evaluable patients had to be recruited and observed for a median period of 5 years to achieve 80% power to identify an improvement from 60% to 67% in EFS after 5 years at 5% significance (ie, one sided). Some over-recruitment was allowed to increase the statistical validity of the prospectively planned subgroup comparisons in the strata with four to nine and with 10 or more positive nodes; 558 and 598 patients were required to have 80% power for an anticipated improvement from 60% to 70% and from 45% to 55%, respectively.

Event-related data were estimated according to the method of Kaplan and Meier[17] and were compared between treatment and prognostic groups by using the log-rank test.[18] For multivariate analysis, a Cox proportional hazard model was applied. Either Fisher's exact test or an exact version of the Cochran-Armitage trend test was used to compare toxicity scores. All tests except for the primary hypothesis were two sided and of explorative nature (ie, hypothesis generating). This included all subgroup analyses and multivariate models.

RESULTS

Patient Characteristics

Between November 1998 and April 2003, a total of 1,284 patients were randomly assigned to a treatment arm. From the 658 and 626 patients allocated to arm A (IDD-ETC) and arm B (EC→T), respectively, 641 (97%) and 611 (98%) were evaluable for the primary end point analysis (CONSORT diagram, Fig 1). Three patients in the IDD-ETC arm were considered noneligible for the following reasons: cardiac arrhythmia (LOWN IIIB, Bigeminus), liver metastasis present before random assignment, and severe wound healing as a complication. All three patients were excluded from the analysis of the primary end point.

The treatment arms were well balanced with respect to demographic and prognostic factors (Table 1). In both study arms, the median number of positive axillary nodes was eight, and 42% of the patients had 10 or more involved axillary lymph nodes.

Table 1. Baseline Demographic and Clinical Characteristics of Patients

Characteristic	Patients: Dose-Dense Sequential Chemotherapy (n = 643) No.	%	Patients: Conventional Chemotherapy (n = 612) No.	%
Age, years				
Median	51		51	
Range	28-67		21-72	
Premenopausal	306	48	292	48
ECOG performance status > 0	113	18	116	19
Breast-conserving surgery	274	43	308	50
Extent of axillary surgery				
Level I	—	—	3	0
Level II	495	78	462	77
Level III	138	22	138	23
Tumor stage				
pT1	181	28	199	33
pT2	362	56	330	54
pT3	96	15	80	13
pT4	4	1	3	0
Lymph nodes, median				
Examined	20		20	
Positive	8		8	
No. of positive nodes				
4-9	376	58	358	58
≥ 10	267	42	254	42
Grade				
1	15	2	11	2
2	310	49	293	48
3	310	49	302	50
Receptor status				
ER positive	465	73	438	72
PR positive	438	69	411	68
HER2 status				
Positive	162	25	150	25
Negative	371	58	346	57
Not done	107	17	115	19
Hormonal treatment for ER-/PR-positive patients				
Tamoxifen for 5 years	293	59	301	64
AI after 2-3 years of tamoxifen	109	21.8	83	17.7
No hormonal treatment	87	17.4	65	13.9
Other	10	2	18	3.8
Radiation therapy				
Whole breast	277	49	308	54
Whole breast plus boost	204	36	226	39
Internal mammary nodes	210	37	201	35
Supra- and infraclavicular	467	81	483	84
Axillary field	305	53	294	51
Postmastectomy chest wall	311	54	279	49

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; AI, aromatase inhibitor.

Treatment

All planned cycles of chemotherapy could be administered to 91% of patients in the conventional arm and to 84% in the IDD arm. The predominant causes for treatment discontinuation in the IDD-ETC arm were toxicity (65% of withdrawals) and patient preference (20%). Relapse during treatment occurred more frequently with conventional dosing than intense dosing (ie, 11 v three patients).

More than 97% of the women in the conventional arm received the full protocol dose per administered cycles. In the IDD-ETC arm, we observed virtually no dose reduction with epirubicin (mean dose per cycle, 149 mg/m^2) and with paclitaxel (mean dose per cycle, 223 mg/m^2), and we observed only a minor dose reduction with cyclophosphamide (mean dose per cycle, 2,444 mg/m^2). Overall, 93% of all cycles administered in the IDD-ETC arm were applied at full dose. Both myelosuppression and nonhematologic toxicity were reported as reasons for reduction in roughly equal frequency. Treatment delays occurred in 16% of the IDD and in 12% of the conventional cycles. However, more than 50% of delays were reported to be caused by logistical problems (eg, bank holidays) or patient preference rather than required by toxicity.

Hematologic Toxicity

Hematologic toxicity was more pronounced in the IDD arm (Appendix Table A1, online only). The difference was highly significant ($P < .001$) with respect to all three peripheral-blood cell lines. In the IDD-ETC arm, the incidence was highest during treatment with cyclophosphamide and was modest with paclitaxel therapy. All patients had full recovery of their peripheral-blood counts at the end of treatment.

Thrombocytopenia was no major problem in either arm. At least one episode of febrile neutropenia was recorded in only 5% of the patients overall; 7% was observed in the IDD-ETC arm, and 2% was observed in the EC→T arm ($P < .001$). Only six patients (1%) in the EC→T arm compared with 127 patients (20%) in the IDD-ETC arm received red blood cell transfusions ($P < .001$ by Fisher's exact test). The sub–random assignment with or without epoetin alfa had no effect on EFS or OS in the IDD-ETC arm.[19] Detailed results will be published separately. We observed no toxic death during treatment in either of the arms.

Nonhematologic Toxicity

Nonhematologic toxicity occurred significantly more often in the IDD-ETC arm, but the incidence of National Cancer Institute grades 3 and 4 toxicity was quite low and was clinically acceptable (Appendix Table A2, online only). In both study arms, no grade 3 congestive heart failure was observed.

Prolonged peripheral neuropathy was generally rare and of mild to moderate severity. After a median follow-up duration of 4 years, 2% of the patients in the IDD arm compared with no patients in the conventional arm reported persisting grades 1 or 2 neurotoxicity.

Secondary neoplasms were reported in 11 patients (0.9%) during follow-up. With eight events, the frequency was higher in the IDD arm, but this difference did not reach statistical significance ($P = .23$). Four occurrences of acute myeloid leukemia or myelodysplastic syndrome (MDS) occurred in the IDD-ETC arm versus none in the standard arm.

Efficacy

After a median follow-up period of 62 months, 408 events and 253 deaths have been recorded. EFS (182 *v* 226 events) and OS (114 *v* 139 events) both favored significantly the IDD-ETC arm. Figure 3A shows the intent-to-treat Kaplan-Meier analysis of EFS according to random assignment. EFS was significantly longer for the IDD-ETC arm ($P < .001$ by log-rank test, one sided; hazard ratio [HR], 0.72; 95% CI, 0.59 to 0.87). The HR was 0.69 (95% CI, 0.57 to 0.84) after analysis was adjusted for major prognostic baseline parameters in a multivariate model. At 5 years, the estimated EFS rates for the IDD-ETC arm and the conventional arm were 70% (95% CI, 68% to 75%) versus 62% (95% CI, 59% to 67%), respectively. For all patients, bone (42%), liver (33%), and lung (18%) were the most frequent sites of recurrence. Brain metastases occurred in 9% of the patients.

The risk of mortality was reduced by 24% (HR, 0.76; 95% CI, 0.59 to 0.97; $P = .029$ by log-rank test, two sided). The 5-year survival rates according to the Kaplan-Meier estimation were 82% (95% CI, 79% to 85%) in the IDD-ETC arm compared with 77% (95% CI, 74% to 81%) in the standard arm (Fig 3B).

Prognostic/Predictive Factors

The results of univariate analyses regarding the effect of different potential prognostic factors on EFS are listed in Table 2. Lower number of positive nodes, smaller primary tumor size, positive hormone receptor status, negative human epidermal growth factor receptor 2 (HER2) status, a lower grade (ie, grades 1 and 2), and tumor marker values (ie, carcinoembryonic antigen and CA 15-3) within the normal range

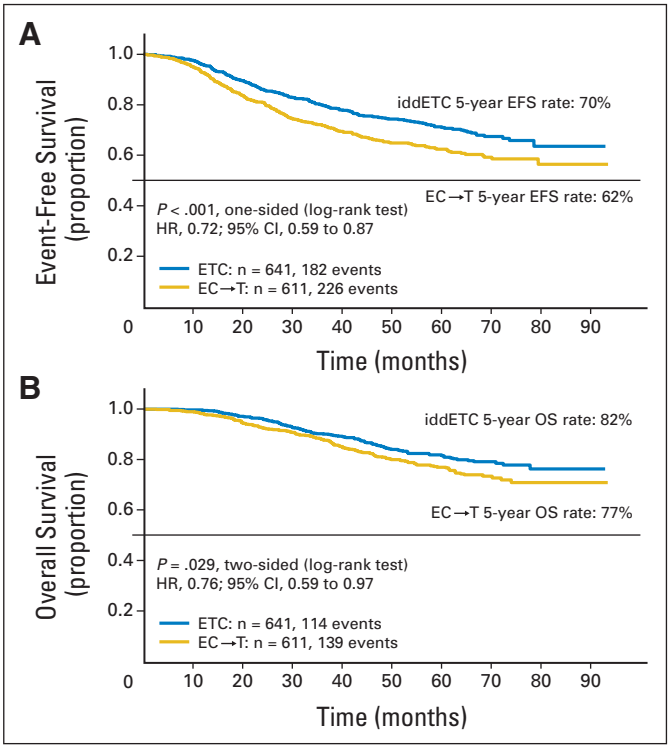

Fig 3. Event-free survival (EFS) and overall survival (OS) by treatment arm: (A) EFS; (B) OS. iddETC, intense dose-dense epirubicine, paclitaxel, and cyclophosphamide; EC→T, epirubicin and cyclophosphamide followed by paclitaxel; HR, hazard ratio.

Table 2. Univariate and Multivariate Analysis of Event-Free Survival

Variable	Univariate *P*	Multivariate (reduced model) *P*	HR	95% CI
Treatment arm, dose-dense *v* conventional	< .001*	< .001	0.69	0.57 to 0.84
Menopausal status	.79	—	—	—
pT 2/3 *v* pT 1	< .001	.0023	1.44	1.14 to 1.81
≥ 10 *v* 4-9 positive nodes	< .001	< .001	1.66	1.36 to 2.03
Grade, 3 *v* 1/2	< .001	< .001	1.57	1.27 to 1.94
Hormone receptor status†	< .001	< .001	0.60	0.48 to 0.74
HER2	.011	NS	—	—
Baseline hemoglobin, < *v* ≥ 12 g/dL	.35	—	—	—
CEA, normal range *v* elevated‡	< .001	—	—	—
CA 15-3, normal range *v* elevated‡	.059	—	—	—

NOTE. Cells with — indicate variables not in the model; tumor markers were not in the model because of high frequency of missing values. Cell with no independent significance was dropped from the model.

Abbreviations: HER2, human epidermal growth factor receptor 2; CEA, carcinoembryonic antigen.

*Two sided.

†At least one positive receptor status *v* both negative.

‡Prior to the first cycle of chemotherapy.

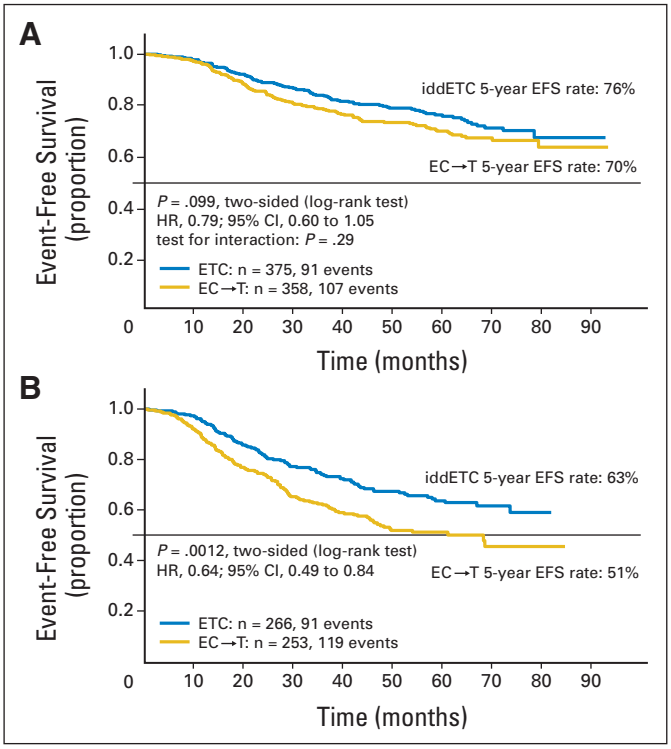

Fig 4. Event-free survival (EFS) by therapy and nodal status: (A) four to nine positive lymph nodes (LNs); (B) 10 or more positive LNs. iddETC, intense dose-dense epirubicine, paclitaxel, and cyclophosphamide; EC→T, epirubicin and cyclophosphamide followed by paclitaxel; HR, hazard ratio.

were associated with superior EFS, whereas menopausal status and baseline hemoglobin had no significant impact. Tumor markers were measured as a baseline test before the first cycle of chemotherapy. Twenty-one of 32 patients with elevated carcinoembryonic antigen levels (> 5 ng/mL) and 56 of 141 patients with elevated CA 15-3 levels (> 25 U/mL) have experienced relapse. All parameters identified by univariate analysis (including the random assignment arm), except for HER2, retained an independent prognostic information in a multivariate Cox model.

In a prospectively planned subgroup analysis of EFS, the treatment arms were compared separately for the two lymph node strata (Figs 4A and 4B). Chemotherapy intensification seems to have a more pronounced effect in the subgroup with the highest tumor load ($P = .0012$), whereas the difference in the group with four to nine positive nodes did not yet meet the preset criterion for significance ($P = .099$). The test for heterogeneity of the treatment effect was not significant ($P = .29$). The impact of randomly assigned treatment on EFS in other major subgroups is shown in Figure 5. There is a clear trend toward a better effect in patients with less favorable tumor biology. However, we could not identify any subgroup in which the IDD regimen did not yield any advantage. For example, patients with HER2-negative as well as estrogen receptor–positive disease showed a statistically significant improvement in EFS. *P* values were .012 and .030 for HER2-negative and HER2-positive disease and were .013 for both patients with ER-negative and ER-positive disease.

DISCUSSION

Dose-dense chemotherapy has become one of the possible standards of adjuvant chemotherapy. This study and the Cancer and Leukemia Group B (CALGB) trial CALGB C9741[8] have independently shown that dose-dense chemotherapy leads to superior EFS and OS in comparison to conventionally dosed chemotherapy. Although we used an equi-effective dose of epirubicin instead of doxorubicin, the regimens in both of the control arms of CALGB C9741 and our study appear to be comparable. Moreover, the median follow-up duration in both trials is 5 years. However, our patient population was different from that of the CALGB C9741 trial. Our study was conducted in patients with high-risk primary breast cancer who had four or more positive axillary lymph nodes (average of eight positive axillary lymph nodes), of which 42% of the patients had 10 or more positive axillary lymph nodes. In contrast, the median number of involved nodes in the CALGB C9741 trial was three, and only 12% had 10 or more involved axillary lymph nodes.

Furthermore, in contrast to the CALGB C9741, which was purely based on the concepts of dose density and sequential application, with total dose of each agents in both regimens equal, the IDD-ETC regimen differed not only by higher dose density but also by a higher total dose than the conventional arm. Even if it remains somewhat uncertain as to which variable contributed most to the improved outcome, the Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) trial appears to be consistent with the hypothesis that dose density matters when using anthracyclines and paclitaxel; thus, the AGO trial represents a confirmatory trial of the CALGB C9741 study. Considering present knowledge, both trials have a suboptimal standard arm, which could not be foreseen when these trials were started. At that time, four cycles of doxorubicin/cyclophosphamide or epirubicin/cyclophosphamide followed by four cycles of paclitaxel at every-3-week intervals, were a modern standard of care in lymph node–positive disease.[6,7] Other studies have suggested that the benefit of taxane-based or dose-dense chemotherapy may be restricted to patients with HER2-positive[20] or steroid hormone receptor–negative disease.[21] Our study also demonstrated a benefit of IDD-ETC in patients with estrogen receptor–positive breast cancer, which was not seen for dose-dense therapy in a retrospective subset analysis of the CALGB C9741 data.[9] The possible reason for this difference could be the higher nodal status of our patient population, which may effectively erase the IDD and HER2/estrogen receptor interaction.

However, not all adjuvant dose-dense trial data were viewed as positive. The GONO-MIG (Gruppo Oncologico Nord Ovest-Mammella InterGruppo) trial compared FU, epirubicin, and cyclophosphamide administered every 3 weeks versus the same regimen given every 2 weeks with granulocyte colony-stimulating factor support.[22] As in the CALGB study, the chemotherapy dose per cycle and total number of cycles were held constant, and only the interval between cycles varied. The difference between these two arms did not reach statistical significance for either recurrence or death. These negative results may be explained by the study design. The GONO-MIG trial applied a substandard version of the FEC regimen (ie, FU at 600 mg/m^2, epirubicin at 60 mg/m^2, and cyclophosphamide at 600 mg/m^2 × six cycles). The total dose of epirubicin in both arms was 360 mg/m^2, which corresponded to only 50% of the total dose in the highly effective Canadian CEF regimen[1] (ie, cyclophosphamide 75 mg/m^2 orally days 1 through 14, epirubicin 60 mg/m^2 days 1 and 8, and FU 500 mg/m^2 intravenously day 1 and 8 for six cycles) or to only 60% of the total dose in the French $FE_{100}C$ regimen (FU 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 for six cycles).[23]

Careful consideration of the potential contribution of both dose density and higher dose may be the way to improve results. This concept is additionally supported by the recently published ECOG/

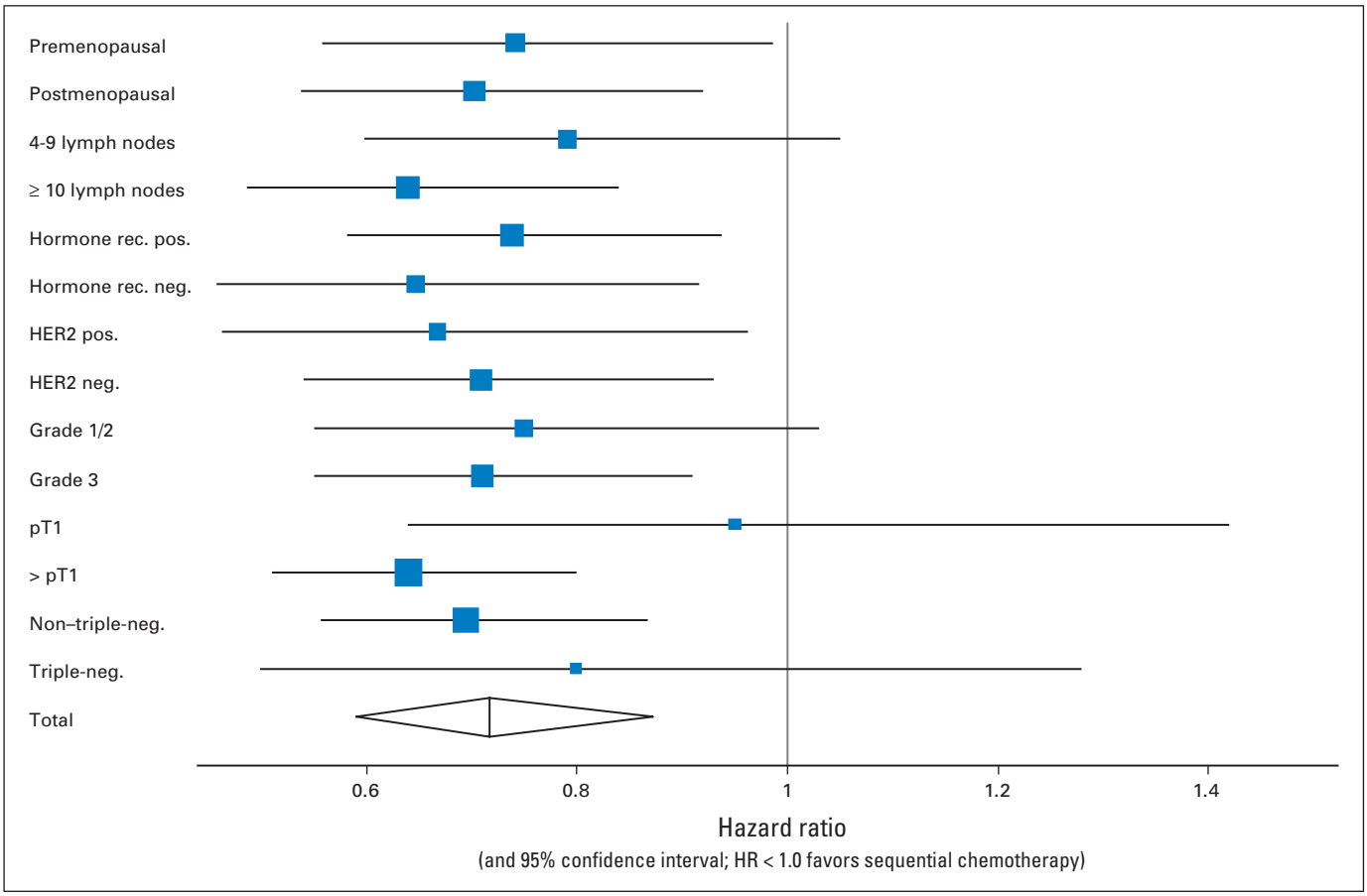

Fig 5. Hazard plot of treatment effect in major subgroups. Rec, receptor; pos, positive; neg, negative; HER2, human epidermal growth factor receptor 2; HR, hazard ratio.

Intergroup trial ECOG 1199, which compared the every-3-week versus weekly administration of paclitaxel or docetaxel after four cycles of doxorubicin/cyclophosphamide.[24] In a prospectively planned subgroup analysis of this four-arm trial, only the weekly paclitaxel application (80 mg/m^2), which was dose dense and higher dose in comparison with the weekly docetaxel arm (35 mg/m^2), showed a significant superior DFS and OS compared with the predefined standard arm (ie, paclitaxel 175 mg/m^2 every 3 weeks).

Four occurrences (0.6% of patients) of secondary leukemia/MDS were reported in the IDD-ETC arm only. This corresponds to published data of anthracycline and (high-dose) cyclophosphamide regimens. With 10 years of follow-up, 5 occurrences (1.4% of patients) of secondary leukemia/MDS were reported for patients receiving the Canadian CEF regimen.[1] The authors found no additional increase of leukemia in comparison with the 5-year follow-up data. Praga et al[25] reviewed 19 adjuvant trials with epirubicin and cyclophosphamide in 2005. Depending on the total dose of both epirubicin and cyclophosphamide, patients had a 8-year cumulative probability of secondary leukemia/MDS ranging between 0.37% and 4.97%.

Given that 42% of the patients had 10 or more positive lymph nodes, with a median number of eight positive lymph nodes, a 5-year OS rate of 82% in the IDD-ETC arm represents, to our knowledge, the best result ever reported in such a high-risk group of patients with breast cancer. Of particular interest is that these survival data were achieved without upfront or first-line therapy with aromatase inhibitors, bisphosphonates, or trastuzumab. The superiority of the IDD-ETC regimen was independent of menopausal, estrogen receptor, and HER2 status.

In conclusion, IDD-ETC is a highly effective, feasible, and safe regimen with manageable toxicity. Even in the upcoming era of targeted therapies, chemotherapy will remain a cornerstone of the adjuvant treatment in patients with breast cancer. Future research should focus on predictive factors for different chemotherapeutic regimens and on combining targeted therapies with dose-dense regimens to continue this incremental advance.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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