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Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741

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Purpose: **Using a 2 × 2 factorial design, we studied the adjuvant chemotherapy of women with axillary node–positive breast cancer to compare sequential doxorubicin (A), paclitaxel (T), and cyclophosphamide (C) with concurrent doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) for disease-free (DFS) and overall survival (OS); to determine whether the dose density of the agents improves DFS and OS; and to compare toxicities.**

Patients and Methods: **A total of 2,005 female patients were randomly assigned to receive one of the following regimens: (I) sequential A × 4 (doses) → T × 4 → C × 4 with doses every 3 weeks, (II) sequential A × 4 → T × 4 → C × 4 every 2 weeks with filgrastim, (III) concurrent AC × 4 → T × 4 every 3 weeks, or (IV) concurrent AC × 4 → T × 4 every 2 weeks with filgrastim.**

Results: **A protocol-specified analysis was performed at a median follow-up of 36 months: 315 patients had experienced relapse or died, compared with 515 expected treatment failures. Dose-dense treatment improved the primary end point, DFS (risk ratio [RR] = 0.74; *P* = .010), and OS (RR = 0.69; *P* = .013). Four-year DFS was 82% for the dose-dense regimens and 75% for the others. There was no difference in either DFS or OS between the concurrent and sequential schedules. There was no interaction between density and sequence. Severe neutropenia was less frequent in patients who received the dose-dense regimens.**

Conclusion: **Dose density improves clinical outcomes significantly, despite the lower than expected number of events at this time. Sequential chemotherapy is as effective as concurrent chemotherapy.**

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ADVANCES IN the adjuvant chemotherapy of primary, operable breast cancer have come both from the introduction of effective agents and from the application of the principles of combination chemotherapy, which underlie much of contemporary oncology.[1,2] Attempts to advance those principles in the treatment of breast cancer by substantial escalation of drug dosage levels have thus far proven unsuccessful.[3,4] Indeed, for the three most useful agents, doxorubicin (A), cyclophosphamide (C), and paclitaxel (T), dose levels greater than 60 mg/m^2, 600 mg/m^2, and 175 mg/m^2 (given over 3 hours), respectively, are not more effective.[5-7] Here we report the initial results of a prospective, randomized study coordinated by the Cancer and Leukemia Group B (CALGB) on behalf of the National Cancer Institute's Breast Intergroup, INT C9741. This study tested two novel concepts based on experimental data and mathematical reasoning. These concepts, dose density and sequential therapy, build on and further develop the theory of combination chemotherapy.[8] This report is prompted by a statistically significant improvement associated with dose density at the protocol-specified analysis.

Dose density refers to the administration of drugs with a shortened intertreatment interval. It is based on the observation that in experimental models, a given dose always kills a certain fraction, rather than a certain number, of exponentially growing cancer cells.[9] Because human cancers in general, and breast cancers in particular, usually grow by nonexponential Gompertzian kinetics, this model has been extended to those situations.[10-14] Regrowth of cancer cells between cycles of cytoreduction is more rapid in volume-reduced Gompertzian cancer models than in exponential models. Hence it has been hypothesized that the more frequent administration of cytotoxic therapy would be a more effective way of minimizing residual tumor burden than dose escalation[8] (Norton L, manuscript submitted for publication). In the INT C9741 trial, the dose-dense schedule

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is accomplished by using granulocyte colony-stimulating factor (filgrastim) to permit every-2-week recycling of the drugs A, T, and C at their optimal dose levels rather than at the conventional 3-week intervals.

Sequential therapy refers to the application of treatments one at a time rather than concurrently. It does not challenge the concept that multiple drugs are needed to maximally perturb cancers that are composed of cells heterogeneous in drug sensitivity.[2] Rather, it hypothesizes that for slow-growing cancers like most breast cancers, it is more important to preserve dose density than to force a combination, especially if that combination would be more toxic and requires dose-reductions or delays in drug administration. If dose density is the same in a sequential combination chemotherapy regimen and a concurrent combination regimen, theoretical considerations indicate that the therapeutic results should be the same, even if the sequential pattern happens to be less toxic[8] (Norton L, manuscript submitted for publication).

PATIENTS AND METHODS

This Intergroup trial, coordinated by the CALGB with participation from the Eastern Cooperative Group, Southwest Oncology Group, and North Central Cancer Treatment Group, was open for patient accrual between September 1997 and March 1999. Its objective was to treat women with primary adenocarcinoma of the breast (including metaplastic and bilateral lesions) and no metastases other than histologically involved axillary lymph nodes (T0 to T3, N1/2, M0).[15] Primary therapy consisted of removal of the entire cancer by a segmental mastectomy (lumpectomy) plus axillary dissection or a modified radical mastectomy with no gross or microscopic invasive tumor at the resection margin. Required laboratory data were limited to an initial bilirubin level within institutional normal limits and, before each cycle of chemotherapy (including the first), a granulocyte count $\geq$ 1,000/μL and platelet count $\geq$ 100,000/μL. Eligible patients also had pretreatment chest radiographs and ECGs. All patients provided written informed consent meeting all federal, state, and institutional guidelines.

Designed for outpatients, all chemotherapy (Fig 1) was given intravenously, starting within 84 days from primary surgery. The study used a 2 $\times$ 2 factorial experimental design to assess the two factors of dose density (2 weeks *v* 3 weeks) and treatment sequence (concurrent *v* sequential) and the possible interaction between them. Patients were assigned with equal probability to one of four treatment regimens: (I) doxorubicin 60 mg/m^2 every 3 weeks for four cycles followed by paclitaxel 175 mg/m^2 every 3 weeks for four cycles followed by cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles; (II) doxorubicin 60 mg/m^2 every 2 weeks for four cycles followed by paclitaxel 175 mg/m^2 every 2 weeks for four cycles followed by cyclophosphamide 600 mg/m^2 every 2 weeks for four cycles, with filgrastim days 3 to 10 of each cycle (a total of seven doses) at 5 μg/kg, which could be rounded to either 300 or 480 μg total dose; (III) doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles followed by paclitaxel 175 mg/m^2 every 3 weeks for four cycles; (IV) doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 2 weeks for four cycles followed by paclitaxel 175 mg/m^2 every 2 weeks for four cycles, with filgrastim days 3 to 10 of each cycle at 5 μg/kg rounded to either 300 or 480 μg total dose. Regimen III was the superior arm of protocol INT C9344, in which it was compared with four cycles of AC every 3 weeks not followed by paclitaxel.[16] Regimen II, the most unconventional dose schedule, being both dose-dense and sequential, had previously been piloted in concept by Hudis et al.[17]

Complete blood cell counts were obtained before each chemotherapy treatment. If the granulocyte count was less than 1,000/μL or the platelet count less than 100,000/μL on the scheduled day, chemotherapy was delayed until those minimal levels were achieved. If there was more than a 3-week delay, the study chair was contacted. Chemotherapy dose modifications were discussed with the study chair. When modifications were indicated because of toxicity, the drug dose was lowered by 25% decrements according to the degree of toxicity.

Radiation therapy, when used, was given after the completion of chemotherapy. Although recommendations regarding this technique were included in the written protocol, investigators were permitted to follow institutional guidelines. It was recommended but not required that tamoxifen 20 mg/d be started within 12 weeks after completion of chemotherapy and be given for 5 years to all premenopausal patients with hormone receptor–positive cancers and to all postmenopausal patients irrespective of receptor status.

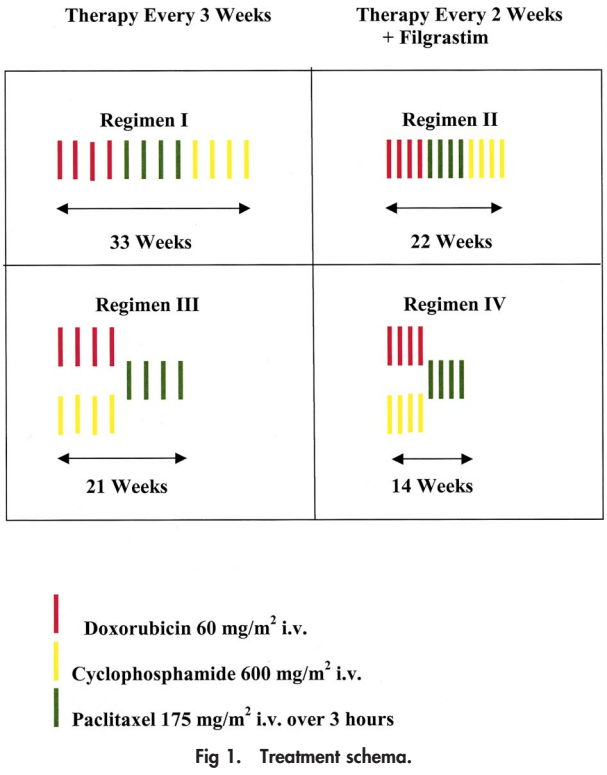

Fig 1. Treatment schema.

Disease-free survival (DFS), which was the primary study end point, was measured from study entry until local recurrence, distant relapse, or death without relapse, whichever occurred first. The spreading of disease to the opposite breast that occurred concurrently with local and/or other distant sites was considered relapse; however, occurrence of disease in the opposite breast in the absence of local and distant recurrence was considered a second primary. All second primaries regardless of site were considered adverse events and not failures in DFS. Surviving patients who were disease-free were censored at the date on which they were last known to be free from their primary breast cancer. The secondary end point of overall survival (OS) was measured from study entry until death from any cause; surviving patients were censored at the date of last contact. Death as a result of acute myelogenous leukemia (AML)/myelodysplastic syndrome (MDS) was considered treatment-related. Target accrual was 1,584 patients over 22 months, with the initial study analysis to be performed at 3 years after completion of accrual. This provided 90% power to detect a 33% difference in hazard for either main effect, assuming an event rate equal to that of an earlier Intergroup (CALGB) trial.[5] Cox proportional hazards regressions with Wald χ^2 tests were used to model and assess the relation between DFS and OS, respectively, and treatment factors with clinical variables. Kaplan-Meier curves with log-rank tests were used to compare the distribution of time with events. Comparisons of two or more proportions used contingency table analysis. Ninety-five percent confidence intervals (CIs) of time-to-event variables used the method of Hosmer and Lemeshow.[18] All *P* values are two-sided. Toxicity grading used the CALGB expanded common toxicity criteria. Patient information was collected on standard CALGB study forms by the CALGB Data Operations unit located in Durham, NC, and entered into the CALGB database. Data were current as of May 2002.

According to National Cancer Institute policy, this study was monitored by an independent Data and Safety Monitoring Committee (DSMC). The trial protocol specified 3 years of follow-up after the last patient accrued, and the DSMC released the results to the CALGB Breast Committee at that time. The study was activated in September 1999 and underwent the first monitoring review in November 1999. Subsequent reviews occurred every 6 months until June 2002,

Table 1. Patient Characteristics and Pretreatment Variables According to Regimen

Characteristic	I		II		III		IV	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Total treated	484	100	493	100	501	100	495	100
Stratification								
No. of positive nodes								
1-3	287	59	292	59	301	60	293	59
4-9	139	29	143	29	142	28	145	29
10+	57	12	58	12	57	11	57	11
Sentinel node dissection	1	< 1	0	0	1	< 1	0	0
Demographics								
Age								
< 40 years	64	13	75	15	84	17	75	15
40-49 years	172	36	172	35	175	35	168	34
50-59 years	166	34	149	30	161	32	163	33
60-69 years	70	14	86	17	64	13	78	16
70+ years	12	3	11	2	17	3	11	2
Menopausal status								
Pre	241	50	237	48	241	49	238	48
Post	235	48	249	51	254	50	247	50
Missing	8	2	7	1	6	1	10	2
ER status								
Negative	163	34	175	35	164	33	160	32
Positive	313	64	311	63	327	65	325	66
Missing	8	2	7	2	10	2	10	2
Tumor size								
≤ 2 cm	185	38	212	43	194	39	199	40
> 2 cm	289	60	271	55	292	58	287	58
Missing	10	2	10	2	15	3	9	2
Surgery								
Lumpectomy	162	33	173	35	185	37	187	37
Mastectomy	312	65	306	62	300	60	301	61
Other	7	1	10	2	11	2	4	1
Unknown	3	1	4	1	5	1	3	1
Tamoxifen								
Received	339	70	350	71	337	67	353	71
Did not receive	145	30	143	29	164	33	142	29
Received								
And premenopausal	160	33	156	32	149	30	153	31
And postmenopausal	173	36	189	38	186	37	192	38
And unknown menopausal	6	1	5	1	2	< 1	8	2

NOTE. Regimen I, sequential doxorubicin → paclitaxel → cyclophosphamide every 3 weeks; regimen II, sequential doxorubicin → paclitaxel → cyclophosphamide every 2 weeks; regimen III, concurrent doxorubicin and cyclophosphamide every 3 weeks followed by paclitaxel every 3 weeks; regimen IV, concurrent doxorubicin and cyclophosphamide every 2 weeks followed by paclitaxel every 2 weeks (see text for details).

Abbreviation: ER, estrogen receptor.

when the DSMB decided to release the data. A structured interim analysis plan included in the protocol was strictly adhered to. The plan specified the timing of the analyses, the adjusted *P* values, and spending function.

RESULTS

Between September 1997 and March 1999, 2,005 volunteer female patients were accrued from CALGB (41%), Eastern Cooperative Oncology Group (30%), Southwest Oncology Group (16%), and North Central Cancer Treatment Group (13%). This total was increased from that planned (1,584) in an attempt to compensate for a faster than expected accrual rate. Thirty-two patients never received any protocol therapy. The 1,973 patients (> 98%) who were treated provide the basis for this report (Table 1). Median patient age was 50 years, 65% had estrogen receptor (ER)-positive tumors, the median number of

Table 2. Multivariate Cox Proportional Hazards Model: Disease-Free Survival (n = 1,973)

Variable	Comparison for Risk Ratio*	Risk Ratio	95% Confidence Interval	*P*
No. of positive nodes†	1 versus 10	0.45	0.57 to 0.44	< .0001
Tumor size, cm†	2 versus 5	0.65	1.27 to 0.78	< .0001
Menopausal status	Post versus pre	0.92	1.17 to 0.74	.54
Estrogen receptor status‡	Positive versus negative	0.30	0.38 to 0.23	< .0001
Sequence	Concurrent versus sequential	0.93	1.17 to 0.74	.58
Density	Every 2 versus every 3 weeks	0.74	0.93 to 0.58	.010
Interaction between density and sequence				.40

*First category names the group at higher risk of failure.

†A square root transformation was used in analyses.

‡Ninety-one percent of patients with estrogen receptor–positive tumors received tamoxifen. Therefore, the benefit of estrogen receptor positivity is confounded with that of tamoxifen.

involved lymph nodes was three, and 12% had 10 or more involved axillary lymph nodes. The regimens were balanced with regard to these and all other major pretreatment variables. The maximum and median follow-up times are 5 and 3 years, respectively. After a median follow-up of 36 months, 315 patients had experienced relapse or died, compared with 515 expected failures under the assumption that both arms would have the event rate we observed in CALGB 8541.[5] The smaller number of failures than expected is partly explained by the rapid accrual rate and partly by the more favorable course of all women in the trial compared with that of women in prior CALGB studies.[5,16]

As Table 2 indicates, DFS was significantly prolonged for the dose-dense regimens (II and IV) compared with the every-3-weeks regimens (I and III; risk ratio [RR] = 0.74; $P = .010$). This dose-density effect remained statistically significant even after adjusting for number of positive nodes, tumor size, menopausal status, and tumor ER status. Treatment sequence was not correlated with DFS ($P = .58$), nor was there a suggestion of an interaction between dose density and treatment sequence ($P = .40$). Figures 2A, 3A, and 4A show the main effects of dose density and treatment sequence and the lack of interaction between the two factors, respectively.

The estimated DFS rates (and 95% CIs) for the dose-dense and conventional 3-week schedules were 97% (95% CI, 96.8% to 97.1%) versus 95% (95% CI, 94.8% to 95.2%) at 1 year, 91% (95% CI, 90.6% to 91.4%) versus 87% (95% CI, 86.5% to 87.5%) at 2 years, 85% (95% CI, 84.5% to 85.5%) versus 81% (95% CI, 80.3% to 81.7%) at 3 years, and 82% (95% CI, 80.7% to 83.3%) versus 75% (95% CI, 73.7% to 76.2%) at 4 years. The first two of these (both the absolute figures and relative difference) will change little with further follow-up. The reason is that all patients have been in the trial for longer than 2 years, and complete data are available for 99% of the patients at 1 year and 92% at 2 years. The 3-year OS was 92% (95% CI, 91.7% to 92.3%) in the dose-dense regimens and 90% (95% CI, 89.6% to 90.4%) for those receiving 3-week treatment. The relative reduction in hazard of recurrence attributed to the dose-dense schedule was 28% at 1 year, 13% at 2 years, 50% at 3 years, and 52% at 4 years. Although these latter estimates have large standard errors (SEs), this suggests that the benefit of dose density continues into the period of longer follow-up.

The overall relative reduction in hazard attributed to dose-dense therapy was 19% for ER-positive tumors and 32% for ER-negative tumors. This difference by ER status (interaction between ER and treatment) is not statistically significant. There were no differences in the pattern of local recurrences for either treatment factor (dose density or sequence) despite differences in time from surgery to local radiation therapy (19 to 37 weeks).

Table 3 shows that OS was significantly prolonged in the dose-dense regimens (RR = 0.69; $P = .013$), even after adjusting for the standard clinical pretreatment variables mentioned previously. Treatment sequence was not significantly correlated with OS ($P = .48$). There was no interaction between density and sequence of treatment ($P = .13$). Figures 2B and 3B show the relation between OS and density and OS and sequence,

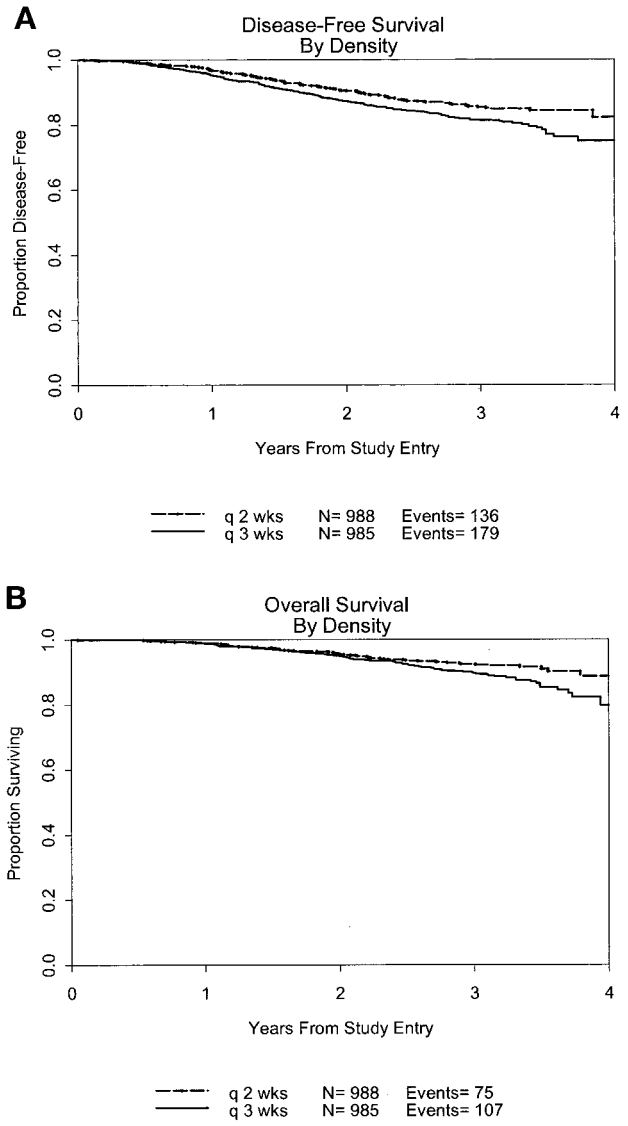

Fig 2. (A) Disease-free survival by dose density; (B) overall survival by dose density.

respectively. Figure 4B shows the lack of interaction between the two factors.

The sites of first recurrence are listed in Table 4. Although this study is not designed for formal comparisons among arms, the pattern of failure was similar among regimens.

Standard nonhematologic toxicity data for grades 3 to 5 were available for 1,962 patients (Table 5). Detailed data regarding dose delay, drug dose received, blood transfusions, hospitalization, and complications were available for 412 patients over 3,973 treatment cycles (Table 6). There were no treatment-related deaths during therapy. There was only one death within the first 6 months of protocol treatment; the cause of death, cerebral infarction, was considered unrelated to treatment. The number of cycle delays was relatively small, ranging from 7% on regimens I and II to 8% and 6% on regimens III and IV, respectively. Of the cycles delayed, 38% of the delays on the every-3-weeks regimens were the result of hematologic toxicity, compared with 15% on the every-2-weeks regimens ($P < .0001$). Dose reductions were infrequent (Table 7). Overall, only

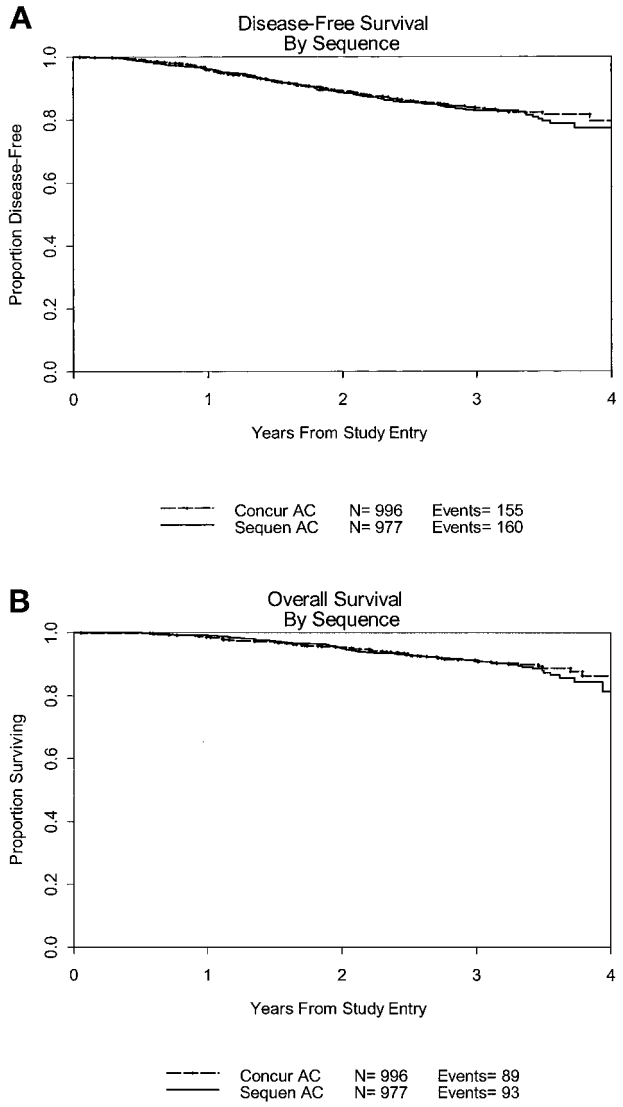

Fig 3. (A) Disease-free survival by sequence; (B) overall survival by sequence.

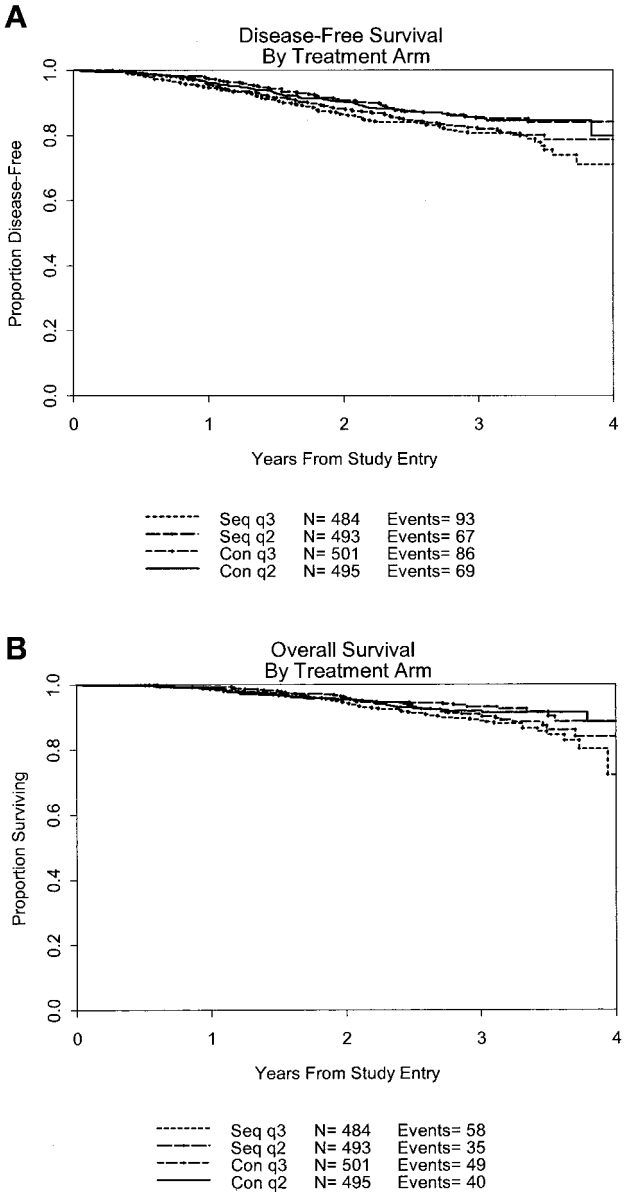

Fig 4. (A) Disease-free survival by treatment arm; (B) overall survival by treatment arm.

3% of patients were hospitalized for febrile neutropenia. Grade 4 granulocytopenia ($< 500/\mu L$) was more frequent on the 3-week regimens compared with the dose-dense regimens (33% *v* 6%; $P < .0001$). Although 13% of patients on the concurrent dose-dense regimen (IV) underwent at least one RBC transfusion, there were no transfusions on the sequential 3-week treatment (I) and less than 4% in each of the other two regimens ($P = .0002$). Grade 3 or greater emesis was significantly more common for the concurrent regimens than for the sequential regimens (7% *v* 3%; $P = .0002$)

Table 3. Multivariate Cox Proportional Hazards Model: Overall Survival (n = 1,973)

Variable	Comparison for Risk Ratio*	Risk Ratio	95% Confidence Interval	*P*
No. of positive nodes†	1 versus 10	0.42	0.57 to 0.32	< .0001
Tumor size, cm†	2 versus 5	1.49	0.67 to 0.52	.0019
Menopausal status	Post versus pre	0.90	1.21 to 0.66	.50
Estrogen receptor status‡	Positive versus negative	0.17	0.24 to 0.12	< .0001
Sequence	Concurrent versus sequential	0.89	1.20 to 0.66	.48
Density	Every 2 versus every 3 weeks	0.69	0.92 to 0.50	.013
Interaction between density and sequence				.13

*First category names the group at higher risk of failure.

†A square root transformation was used in analyses.

‡Ninety-one percent of patients with estrogen receptor–positive tumors received tamoxifen. Therefore, the benefit of estrogen-receptor positivity is confounded with that of tamoxifen.

Table 4. Site(s) of First Relapse by Regimen

	I		II		III		IV	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Total failures	93	100	67	100	86	100	69	100
Site of failure								
Local only	23	25	18	27	19	22	14	20
Distant only	58	62	44	66	56	65	46	67
Local and distant concurrently	12	13	5	7	11	13	9	13

NOTE. Regimen I, sequential doxorubicin → paclitaxel → cyclophosphamide every 3 weeks; regimen II, sequential doxorubicin → paclitaxel → cyclophosphamide every 2 weeks; regimen III, concurrent doxorubicin and cyclophosphamide every 3 weeks followed by paclitaxel every 3 weeks; regimen IV, concurrent doxorubicin and cyclophosphamide every 2 weeks followed by paclitaxel every 2 weeks (see text for details).

There have been six treatment-related deaths (Table 8), all occurring between 23 and 41 months after the beginning of treatment. These include one doxorubicin-related cardiomyopathy, one case of MDS, and four cases of AML, all distributed without pattern among the four regimens.

Thus far, less than 2% of patients reported late significant cardiac toxicity requiring treatment. Patients receiving the every-3-weeks regimens had a slightly higher incidence of late cardiotoxicity than those receiving the every-2-weeks regimens (2% *v* 1%; $P = .11$) Severe postchemotherapy neurotoxicity was rare

Table 5. Major Toxicities That Occurred During Protocol Treatment

		Grade of Toxicity						
		3*		4†		5‡		
	Regimen	No. of Patients	%	No. of Patients	%	No. of Patients	%	Total
WBC	I	2	0	4	1	0	0	479
	II	0	0	1	0	0	0	490
	III	3	1	57	11	0	0	500
	IV	1	0	28	6	0	0	493
Platelets	I	0	0	1	0	0	0	479
	II	0	0	0	0	0	0	490
	III	2	0	0	0	0	0	500
	IV	1	0	3	0	0	0	493
Platelet transfusion	I	0	0	0	0	0	0	479
	II	0	0	0	0	0	0	490
	III	0	0	0	0	0	0	500
	IV	0	0	0	0	0	0	493
Hemoglobin	I	0	0	0	0	0	0	479
	II	0	0	1	0	0	0	490
	III	1	0	0	0	0	0	500
	IV	0	0	1	0	0	0	493
Granulocytes/bands	I	0	0	113	24	0	0	479
	II	1	0	14	3	0	0	490
	III	0	0	214	43	0	0	500
	IV	1	0	46	9	0	0	493
Nausea	I	22	5	1	0	0	0	479
	II	34	7	1	0	0	0	490
	III	41	8	3	1	0	0	500
	IV	41	8	0	0	0	0	493
Vomiting	I	10	2	4	1	0	0	479
	II	14	3	4	1	0	0	490
	III	32	6	8	2	0	0	500
	IV	18	4	12	2	0	0	493
Diarrhea	I	5	1	1	0	0	0	479
	II	8	2	4	1	0	0	490
	III	7	1	5	1	0	0	500
	IV	5	1	0	0	0	0	493
Stomatitis	I	5	1	0	0	0	0	479
	II	4	1	2	0	0	0	490
	III	14	3	0	0	0	0	500
	IV	9	2	4	1	0	0	493
Cardiac function	I	5	1	1	0	0	0	479
	II	4	1	0	0	0	0	490
	III	1	0	1	0	0	0	500
	IV	0	0	1	0	0	0	493

Table 5. Major Toxicities That Occurred During Protocol Treatment (Cont'd)

		Grade of Toxicity						
		3*		4†		5‡		
	Regimen	No. of Patients	%	No. of Patients	%	No. of Patients	%	Total
Other cardiac	I	2	0	0	0	0	0	479
	II	0	0	0	0	0	0	490
	III	0	0	0	0	0	0	500
	IV	1	0	0	0	0	0	493
Phlebitis/thrombosis	I	3	1	0	0	0	0	479
	II	4	1	0	0	0	0	490
	III	3	1	0	0	0	0	500
	IV	4	1	0	0	0	0	493
Sensory	I	21	4	0	0	0	0	479
	II	19	4	1	0	0	0	490
	III	25	5	2	0	0	0	500
	IV	19	4	0	0	0	0	493
Motor	I	4	1	0	0	0	0	479
	II	4	1	0	0	0	0	490
	III	8	2	1	0	0	0	500
	IV	5	1	0	0	0	0	493
Pain	I	19	4	0	0	0	0	479
	II	33	7	1	0	0	0	490
	III	31	6	3	1	0	0	500
	IV	46	9	1	0	0	0	493
Skin	I	8	2	1	0	0	0	479
	II	15	3	3	1	0	0	490
	III	2	0	0	0	0	0	500
	IV	11	2	1	0	0	0	493
Myalgias/arthralgias	I	23	5	0	0	0	0	479
	II	25	5	0	0	0	0	490
	III	25	5	2	0	0	0	500
	IV	26	5	0	0	0	0	493
Infection	I	14	3	1	0	0	0	479
	II	19	4	0	0	0	0	490
	III	27	5	0	0	0	0	500
	IV	13	3	2	0	0	0	493

NOTE. Regimen I, sequential doxorubicin → paclitaxel → cyclophosphamide every 3 weeks; regimen II, sequential doxorubicin → paclitaxel → cyclophosphamide every 2 weeks; regimen III, concurrent doxorubicin and cyclophosphamide every 3 weeks followed by paclitaxel every 3 weeks; regimen IV, concurrent doxorubicin and cyclophosphamide every 2 weeks followed by paclitaxel every 2 weeks (see text for details).

*Severe toxicity.

†Life-threatening toxicity.

‡Lethal toxicity.

overall but more frequent in the concurrent chemotherapy than in the sequential regimens (4% *v* 2%; $P = .0050$).

Fifty-eight patients have developed second primaries (Table 9), including 11 cases of AML or MDS (inclusive of deaths) diagnosed from 10 to 42 months after study entry, 18 invasive breast cancers, and three cases of ductal carcinoma-in-situ, all distributed without pattern among the four regimens. The 3-year incidence of AML or MDS was 0.18%. This is similar to a prior Intergroup trial (0.17%) for a similar patient population at the same median follow-up.[16] The incidence of leukemia does not

Table 6. Complications During Treatment According to Regimen

	I		II		III		IV	
Complication	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Total with data	103	100	101	100	104	100	104	100
Dose reduction								
During doxorubicin	7	7	5	5	1	1	3	3
During cyclophosphamide	1	1	3	3	5	5	5	5
During paclitaxel	1	1	7	7	4	4	5	5
RBC transfusion	0	0	10	2	15	3	64	13
Hospitalized for febrile neutropenia	14	3	10	2	25	5	10	2

NOTE. Regimen I, sequential doxorubicin → paclitaxel → cyclophosphamide every 3 weeks; regimen II, sequential doxorubicin → paclitaxel → cyclophosphamide every 2 weeks; regimen III, concurrent doxorubicin and cyclophosphamide every 3 weeks followed by paclitaxel every 3 weeks; regimen IV, concurrent doxorubicin and cyclophosphamide every 2 weeks followed by paclitaxel every 2 weeks (see text for details).

Table 7. Dose Reductions According to Regimen

Dose Reduction	I		II		III		IV	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Total with dose data	103	100	101	100	104	100	104	100
During doxorubicin	7	7	5	5	1	1	3	3
During cyclophosphamide	1	1	3	3	5	5	5	5
During paclitaxel	1	1	7	7	4	4	5	5

NOTE. Regimen I, sequential doxorubicin → paclitaxel → cyclophosphamide every 3 weeks; regimen II, sequential doxorubicin → paclitaxel → cyclophosphamide every 2 weeks; regimen III, concurrent doxorubicin and cyclophosphamide every 3 weeks followed by paclitaxel every 3 weeks; regimen IV, concurrent doxorubicin and cyclophosphamide every 2 weeks followed by paclitaxel every 2 weeks (see text for details).

seem to have been influenced by filgrastim. Dose-dense chemotherapy significantly reduced contralateral breast cancer (0.3% *v* 1.5%; $P = .0004$).

DISCUSSION

Previous trials have shown that adding new, effective drugs sequentially to adjuvant treatment regimens can improve survival in patients with early-stage breast cancer.[16,19] In addition, as predicted by theory, sequential chemotherapy has proven superior to a strictly alternating pattern.[14,20] A recently reported trial of sequential A → C versus concurrent AC in the adjuvant setting demonstrated no therapeutic differences, with more toxicity in the sequential arm, but there were by intention major differences between the arms in the dose levels of each drug.[21] Interpretation of this latter trial is complicated by considerations of dose response and the seeming lack of incremental benefit for A and C above certain dose thresholds.[5,6] The prospective, randomized comparison of sequential combination chemotherapy with concurrent combination chemotherapy using the same agents at the same dose levels and the same dose densities has never before been performed. In INT C9741, this comparison was accomplished by testing AC → T versus A → T → C, with an additional manipulation of testing each schedule at two different dose densities, in a 2 × 2 factorial design.

At 3 years after completion of accrual, the total number of relapses was lower than anticipated in this protocol-specified analysis. We speculate that this may be related in part to greater use of tamoxifen in this trial compared with in CALGB 8541 and possibly to a stage shift—within stage—as a result of improved mammographic screening. The patients treated with standard AC → T every 3 weeks in C9741 had fewer relapses at the same follow-up point than patients treated with standard AC → T in 9344, as reported by Henderson et al.[16]

The DFS in this study has sufficiently matured at 1 and 2 years of follow-up so that the statistically significant improvement resulting from dose density at 1 and 2 years will not be lost with further observation. However, the observed survival benefit of dose density occurs beyond 2 years and therefore is subject to greater change than that for DFS. On the other hand, OS benefit emerging later than DFS benefit is biologically tenable and adds credence to the observed survival benefit.

The DFS and OS advantages of dose density were not accompanied by an increase in toxicity. Indeed, the use of filgrastim in the dose-dense regimens resulted in a statistically significant decrease in granulocyte toxicity. However, the low rate of hospitalization and the absence of mortality during chemotherapy illustrate the safety of all four treatment regimens. The low rate of neutropenic sepsis also supports the safety of using a baseline granulocyte count of 1,000/μL

Table 8. Treatment-Related Deaths (n = 6)

Regimen	Survival (months)	Cause of Death
I	30	Heart failure
I	40	AML
I	41	AML
II	23	AML
III	30	MDS
III	39	Infection secondary to AML

NOTE. Regimen I, sequential doxorubicin → paclitaxel → cyclophosphamide every 3 weeks; regimen II, sequential doxorubicin → paclitaxel → cyclophosphamide every 2 weeks; regimen III, concurrent doxorubicin and cyclophosphamide every 3 weeks followed by paclitaxel every 3 weeks; regimen IV, concurrent doxorubicin and cyclophosphamide every 2 weeks followed by paclitaxel every 2 weeks (see text for details).

Abbreviations: AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome.

Table 9. Second Primaries According to Regimen

	I (no. of patients)	II (no. of patients)	III (no. of patients)	IV (no. of patients)
Total treated	484 (100%)	493 (100%)	501 (100%)	495 (100%)
Total with second primary	16 (3%)	16 (3%)	12 (2%)	14 (3%)
Contralateral breast	9	2	6	1
DCIS	1	1	0	1
Cervix	1	0	0	1
Ovary	0	1	0	0
Endometrium	0	1	0	1
AML/MDS	2	3	4	2
Basal/squamous	0	3	1	2
Melanoma	1	1	0	1
Lung	0	2	1	0
Thyroid	0	0	0	2
Colon	0	0	0	1
Intestine	0	0	0	1
Bladder	0	0	0	1
Renal	2	0	0	0
Pancreas	0	1	0	0
Pituitary	0	1	0	0

NOTE. Regimen I, sequential doxorubicin → paclitaxel → cyclophosphamide every 3 weeks; regimen II, sequential doxorubicin → paclitaxel → cyclophosphamide every 2 weeks; regimen III, concurrent doxorubicin and cyclophosphamide every 3 weeks followed by paclitaxel every 3 weeks; regimen IV, concurrent doxorubicin and cyclophosphamide every 2 weeks followed by paclitaxel every 2 weeks (see text for details).

Abbreviations: DCIS, ductal carcinoma-in-situ; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome.

(rather than the traditional 1,500/μL) for administering chemotherapy. The use of the lower limit also may account for the infrequent treatment delays.

At present, these data are consistent with mathematical predictions that dose density would improve therapeutic results and that sequential chemotherapy that maintains dose density would preserve efficacy while reducing toxicity. Several caveats are appropriate. The results might be drug- and disease-specific, the maximum follow-up of 5 years is still relatively short, and treatment-related patterns of late recurrence (including local recurrence) and toxicity may yet emerge. Also, confidence in the OS benefits at longer follow-up of a dose-dense schedule remains to be firmly established. The results of this trial are also limited by the fact that the rates of radiation across treatment arms have not yet been collated.

The cost/benefit ratio must be carefully considered, as filgrastim adds expense. Compared with standard treatment, it can add thousands of dollars to the chemotherapy regimen. Other negatives associated with filgrastim treatment may include mild/moderate myalgias and arthralgias as well as the inconvenience of 7 days of injections per course.

The statistically significant DFS and OS benefits observed for the dose-dense regimens warrant further research. Oncologists should consider the implications of this study for clinical practice in the context of these data. This data set will continue to be followed using standard statistical methodology, and further reports will be generated.

Our results indicate interesting directions for further research. For example, sequential dose-dense single-agent therapy could permit the rapid integration of new drugs into therapeutic regimens, including biologic agents. Shorter intertreatment intervals (ie, beginning re-treatment as soon as the granulocyte count reaches 1,000/μL, rather than at a fixed time interval) might be investigated. Quality of life for patients receiving such treatments might also be beneficially explored. Furthermore, research into the biologic etiology of Gompertzian growth and the molecular mechanisms of its perturbation could be used to hypothesize new, empirically verifiable dose-schedule manipulations.

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