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.

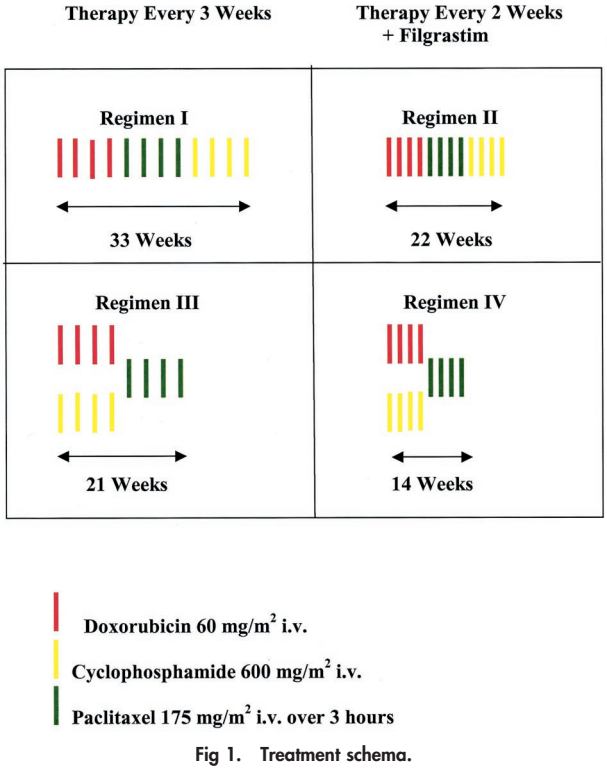

Fig 1. Treatment schema.

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 1997 and underwent the first monitoring review in November 1998. 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

Table 2. Multivariate Cox Proportional Hazards Model: Disease-Free Survival (n = 1892)

Variable	Comparison for Risk Ratio*	Risk Ratio	95% Confidence Interval	*P*
Number of positive nodes†	1 versus 10	0.45	0.36 to 0.57	< .0001
Tumor size†	2 versus 5	0.65	0.54 to 0.79	< .0001
Menopausal status	Post versus Pre	0.93	0.74 to 1.18	.54
Estrogen receptor status‡	Positive versus negative	0.30	0.24 to 0.38	< .0001
Sequence	Concurrent versus sequential	0.93	0.75 to 1.18	.58
Dose density	q2 versus q3	0.74	0.59 to 0.93	.010
Interaction	—	—	—	.40

*The first category names the group at lower 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.

this report (Table 1). Median patient age was 50 years, 65% had estrogen receptor (ER)-positive tumors, the median number of 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

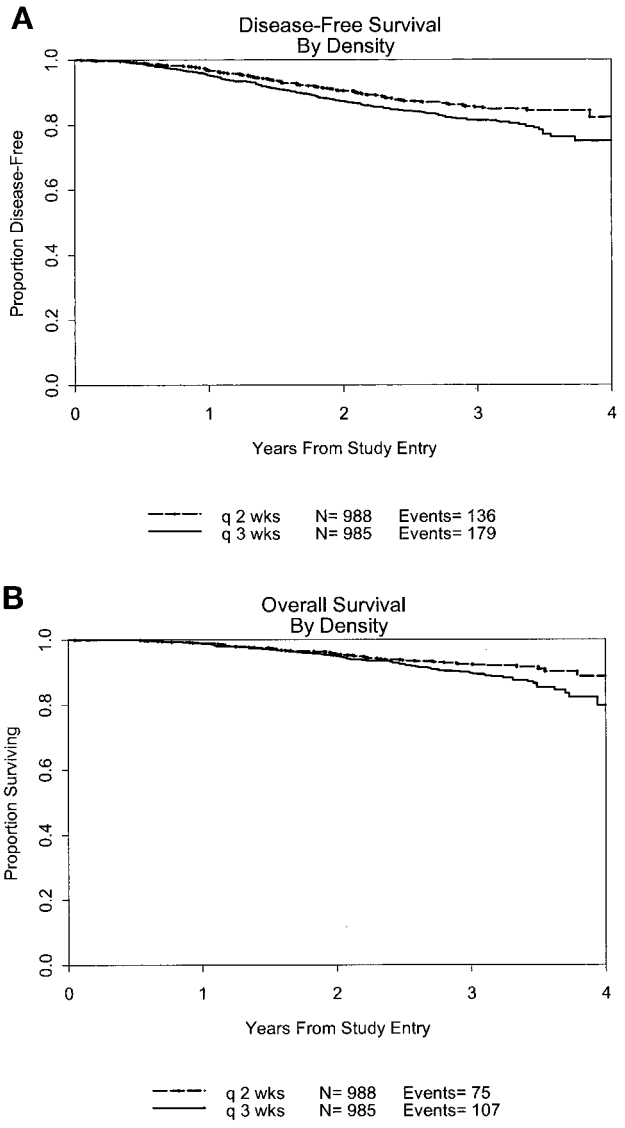

Fig 2. (A) Disease-free survival by dose density; (B) overall survival by dose density.

show the relation between OS and density and OS and sequence, 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 ($P <$

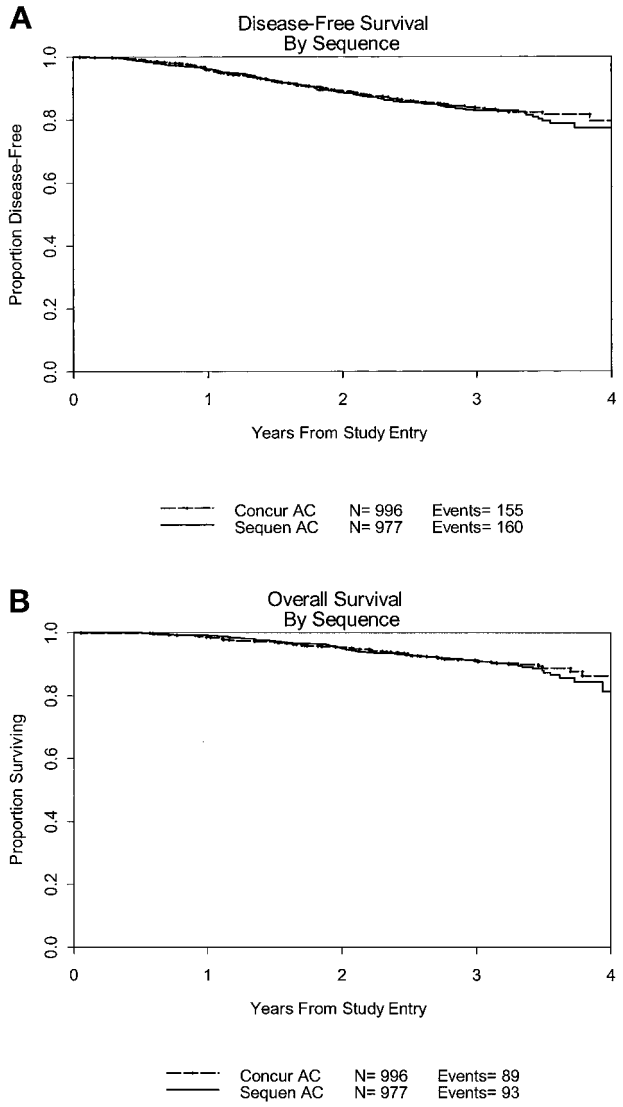

Fig 3. (A) Disease-free survival by sequence; (B) overall survival by sequence.

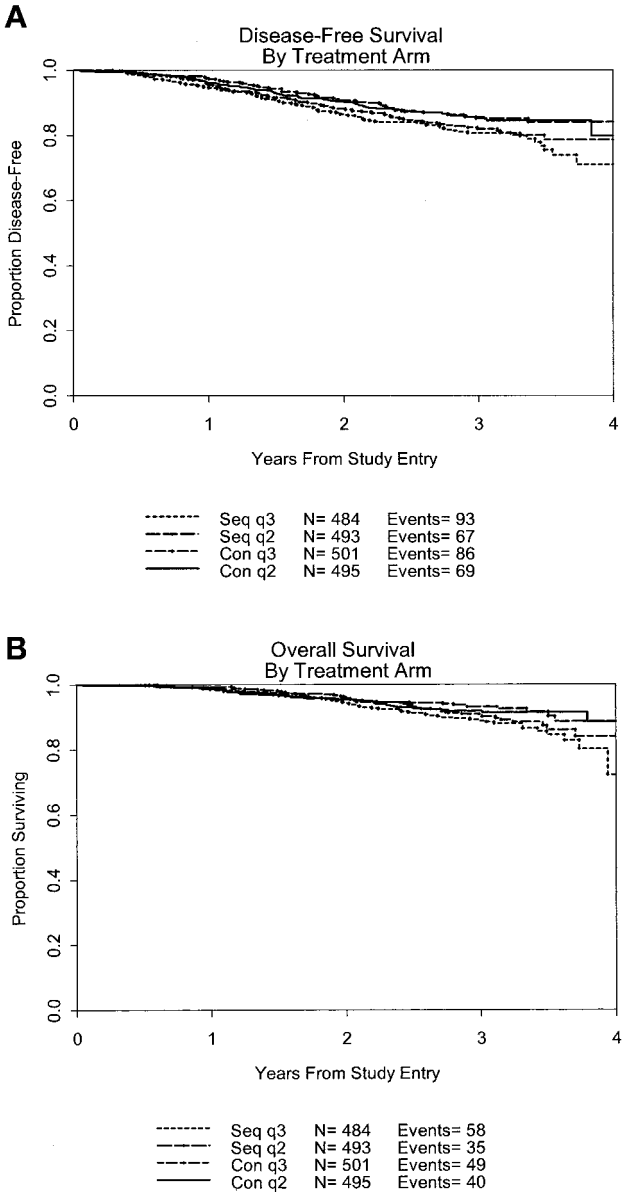

Fig 4. (A) Disease-free survival by treatment arm; (B) overall survival by treatment arm.

.0001). Dose reductions were infrequent (Table 7). Overall, only 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

Table 3. Multivariate Cox Proportional Hazards Model: Overall Survival (n = 1892)

Variable	Comparison for Risk Ratio*	Risk Ratio	95% Confidence Interval	*P*
Number of positive nodes†	1 versus 10	0.43	0.32 to 0.57	< .0001
Tumor size†	2 versus 5	0.67	0.52 to 0.86	.0019
Menopausal status	Post versus Pre	0.90	0.67 to 1.22	.50
Estrogen receptor status‡	Positive versus negative	0.18	0.13 to 0.25	< .0001
Sequence	Concurrent versus sequential	0.89	0.66 to 1.20	.48
Dose density	q2 versus q3	0.69	0.50 to 0.93	.013
Interaction	—	—	—	.13

*The first category names the group at lower risk of death.

†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).

(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)

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*

Table 5. Major Toxicities That Occurred During Protocol Treatment

	Grade of Toxicity						
	3		4		5		
	n	%	n	%	n	%	Total No.
WBC							
Arm 1 (A → T → C q 3 weeks)	2	—	4	1	0	0	479
Arm 2 (A → T → C q 2 weeks)	0	0	1	—	0	0	490
Arm 3 (AC → T q 3 weeks)	3	1	57	11	0	0	500
Arm 4 (AC → T q 2 weeks)	1	—	28	6	0	0	493
Platelets							
Arm 1 (A → T → C q 3 weeks)	0	0	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	0	0	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	2	—	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	1	—	3	—	0	0	493
Hemoglobin							
Arm 1 (A → T → C q 3 weeks)	0	0	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	0	0	1	—	0	0	490
Arm 3 (AC → T q 3 weeks)	1	—	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	0	0	1	—	0	0	493
Granulocytes/bands							
Arm 1 (A → T → C q 3 weeks)	0	0	113	24	0	0	479
Arm 2 (A → T → C q 2 weeks)	1	—	14	3	0	0	490
Arm 3 (AC → T q 3 weeks)	0	0	214	43	0	0	500
Arm 4 (AC → T q 2 weeks)	1	—	46	9	0	0	493
Nausea							
Arm 1 (A → T → C q 3 weeks)	22	5	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	34	7	1	—	0	0	490
Arm 3 (AC → T q 3 weeks)	41	8	3	1	0	0	500
Arm 4 (AC → T q 2 weeks)	41	8	0	0	0	0	493
Vomiting							
Arm 1 (A → T → C q 3 weeks)	10	2	4	1	0	0	479
Arm 2 (A → T → C q 2 weeks)	14	3	4	1	0	0	490
Arm 3 (AC → T q 3 weeks)	32	6	8	2	0	0	500
Arm 4 (AC → T q 2 weeks)	18	4	12	2	0	0	493
Diarrhea							
Arm 1 (A → T → C q 3 weeks)	5	1	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	8	2	4	1	0	0	490
Arm 3 (AC → T q 3 weeks)	7	1	5	1	0	0	500
Arm 4 (AC → T q 2 weeks)	5	1	0	0	0	0	493
Stomatitis							
Arm 1 (A → T → C q 3 weeks)	5	1	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	4	1	2	—	0	0	490
Arm 3 (AC → T q 3 weeks)	14	3	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	9	2	4	1	0	0	493
Cardiac function							
Arm 1 (A → T → C q 3 weeks)	5	1	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	4	1	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	1	—	1	—	0	0	500
Arm 4 (AC → T q 2 weeks)	0	0	1	—	0	0	493

Table 5. Major Toxicities That Occurred During Protocol Treatment (Continued)

	Grade of Toxicity						
	3		4		5		
	n	%	n	%	n	%	Total No.
Other cardiac							
Arm 1 (A → T → C q 3 weeks)	2	—	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	0	0	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	0	0	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	1	—	0	0	0	0	493
Phlebitis/thrombosis							
Arm 1 (A → T → C q 3 weeks)	3	1	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	4	1	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	3	1	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	4	1	0	0	0	0	493
Sensory							
Arm 1 (A → T → C q 3 weeks)	21	4	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	19	4	1	—	0	0	490
Arm 3 (AC → T q 3 weeks)	25	5	2	—	0	0	500
Arm 4 (AC → T q 2 weeks)	19	4	0	0	0	0	493
Motor							
Arm 1 (A → T → C q 3 weeks)	4	1	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	4	1	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	8	2	1	—	0	0	500
Arm 4 (AC → T q 2 weeks)	5	1	0	0	0	0	493
Pain							
Arm 1 (A → T → C q 3 weeks)	19	4	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	33	7	1	—	0	0	490
Arm 3 (AC → T q 3 weeks)	31	6	3	1	0	0	500
Arm 4 (AC → T q 2 weeks)	46	9	1	—	0	0	493
Skin							
Arm 1 (A → T → C q 3 weeks)	8	2	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	15	3	3	1	0	0	490
Arm 3 (AC → T q 3 weeks)	2	—	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	11	2	1	—	0	0	493
Myalgias/arthralgias							
Arm 1 (A → T → C q 3 weeks)	23	5	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	25	5	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	25	5	2	—	0	0	500
Arm 4 (AC → T q 2 weeks)	26	5	0	0	0	0	493
Infection							
Arm 1 (A → T → C q 3 weeks)	14	3	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	19	4	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	27	5	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	13	3	2	—	0	0	493

NOTE. Grade 3, severe toxicity; grade 4, life-threatening toxicity; grade 5, lethal toxicity. Dash stands for <1%.

1%; $P = .11$) Severe postchemotherapy neurotoxicity was rare 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

Table 6. Complications During Treatment

	Treatment Arm							
	Arm 1 (A → T → C q 3 weeks)		Arm 2 (A → T → C q 2 weeks)		Arm 3 (AC → T q 3 weeks)		Arm 4 (AC → T q 2 weeks)	
Complication, patients and cycles	n	%	n	%	n	%	n	%
Total no. patients	103	100	101	100	104	100	104	100
Total no. cycles	1,209	100	1,143	100	818	100	803	100
Patients with any delay	40	39	45	45	41	39	32	31
Cycles delayed	81	7	80	7	68	8	44	6
Patients transfused (RBC)	0	0	3	3	4	4	13	3
Cycles transfused	0	0	10	1	5	1	22	13
Patients hospitalized for febrile neutropenia	3	3	2	2	6	6	2	2
Cycles hospitalized for febrile neutropenia	3	1	5	1	7	1	2	1

Table 7. Dose Reductions According to Regimen

Reduction	Treatment Arm: Arm 1 (A → T → C q 3 weeks) n	%	Arm 2 (A → T → C q 2 weeks) n	%	Arm 3 (AC → T q 3 weeks) n	%	Arm 4 (AC → T q 2 weeks) n	%
Dose reduction								
During Doxorubicin	7	7	5	5	1	1	3	3
During Cyclophosphamide	1	1	3	3	5	5	5	5
During Taxol	1	1	7	7	4	4	5	5

same median follow-up.[16] The incidence of leukemia does not 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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CORRESPONDENCE

Paradigm Shift in Adjuvant Treatment of Receptor Positive Premenopausal Breast Cancer Patients? Not Yet!

To the Editor: We read with great interest the two articles and the editorial in the December 15, 2002 issue of the *Journal of Clinical Oncology*, concerning adjuvant hormonal treatment of breast cancer.[1-3] In both studies, the authors compared a "standard" cyclophosphamide, methotrexate fluorouracil– (CMF-) only treatment arm with goserelin[1] or goserelin plus tamoxifen.[2] According to Jonat et al,[1] "goserelin offers an effective, well-tolerated alternative to CMF chemotherapy in the management of premenopausal patients with ER- [estrogen receptor–] positive and node-positive early breast cancer." According to Jakesz et al,[2] "complete endocrine blockade with goserelin and tamoxifen is superior to standard chemotherapy in premenopausal women with hormone-responsive stage I and II breast cancer." In the editorial commenting on these two studies, Kathleen Pritchard asked, "Is it time for another paradigm shift?"[3]

If this question is asked in the context of the previously mentioned studies, the answer might be, "Not yet." Let us repeat what we all know. First, anthracycline-containing regimens yield superior results, both for recurrence-free survival (absolute difference at 5 years, 3.2%) and overall survival (absolute difference at 5 years, 2.7%).[4] In both the Jonat et al and Jakesz et al studies, the control arm was patients receiving CMF. We know that 4 months of doxorubicin and cyclophosphamide is clearly equivalent to 6 months of CMF[5]; however, we also know that there are regimens that are clearly superior to CMF[6,7] that have been defined in previously reported studies.[8]

Second, tamoxifen was associated with a highly significant improvement in recurrence-free survival (absolute difference at 10 years, 14.9%–15.2%) and in overall survival (absolute difference at 10 years, 5.5%–10.9%) in ER-positive women.[9] In the article by Jonat et al[1] and in the accompanying editorial,[3] it was acknowledged that there were only 177 women with ER-positive disease who were randomly selected to chemotherapy, or to chemotherapy plus tamoxifen in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview. According to the Jonat et al and the accompanying editorial, although widely used in practice, not enough data were available to support the addition of tamoxifen after standard chemotherapy in premenopausal patients, and this argument was used as a justification for lack of tamoxifen use in the control groups. However, both in the recently published studies, as well as in all other studies cited in the editorial that compared ovarian ablation with chemotherapy (mostly with CMF), the chemotherapy plus tamoxifen regimen is apparently lacking. So "177" is better than "zero," and as a general rule, absence of proof does not mean proof of absence. On the other side, Jakesz et al,[2] in addressing the choice of treatment in the control arm, stated that when Austrian Breast and Colorectal Cancer Study Group Trial 5 was launched in 1990, the data of the EBCTGG overview were largely unknown; therefore, CMF-only, the chemotherapeutic regimen of choice at that time, was chosen. However, knowing the data at present, we do not accept CMF without tamoxifen as a "standard" in this group, and so we can not come to the same conclusion of Jakesz et al, who reported that "complete endocrine blockade with goserelin and tamoxifen is superior to standard chemotherapy in premenopausal woman with hormone responsive stage I and II breast cancer". We still do not know what is the "best standard" chemotherapy for lymph node–positive, ER-positive premenopausal breast cancer; however, we absolutely know what is not. CMF without tamoxifen is clearly not a sufficient treatment in this group of patients. Studies with a control arm of anthracycline-based chemotherapy plus tamoxifen are definitely and urgently needed in order that the conclusions of Jakesz et al be better received.

After reading the results of these two trials, we draw a conclusion that is different from those reported. Ovarian ablation with goserelin is equivalent to CMF without tamoxifen, and goserelin plus tamoxifen is more effective than CMF without tamoxifen. If one has a premenopausal patient with ER-positive, lymph node–positive breast cancer, goserelin plus tamoxifen is a good alternative to treating her with intravenous CMF without tamoxifen while achieving the same results. Is there anyone who would treat such a patient with CMF only?

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Can Endocrine Treatment for Hormone-Positive Premenopausal Women With Early Breast Cancer Replace Adjuvant Chemotherapy?

To the Editor: In the December 15, 2002 issue of the *Journal of Clinical Oncology*, Jakesz et al[1] and Jonat et al[2] tried to determine the best

postoperative treatment for hormone-receptor–positive premenopausal women with early breast cancer. Jakesz et al showed that a complete endocrine blockade with 3 years of receiving gosorelin and 5 years receiving tamoxifen was more effective than chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF). Relapse-free survival and local recurrence-free survival were significantly in favor of the endocrine therapy, and there was a trend in favor of the endocrine treatment for overall survival, but this was not statistically significant.

Jonat et al compared 2 years of receiving gosorelin with adjuvant CMF therapy. Disease-free survival was identical for patients with estrogen-receptor–positive tumors.

Both studies were well performed, but neither group mentioned the *neu*/*erb*B-2 overexpression in their series. They both used CMF chemotherapy as their control arm. While some studies have shown that *neu*/*erb*B-2 overexpression is associated with less benefit from CMF chemotherapy,[3,4] the overexpression of *neu*/*erb*B-2 has also been shown to be associated with relative resistance to hormone therapies.[5,6] There is, however, some discrepancy in other reports on the overexpression of this predictive marker and response to endocrine treatment.[7] An uneven distribution of *neu*/*erb*B-2 overexpression might have influenced the outcomes of both studies.

Predictive markers such as *neu*/*erb*B-2 overexpression should be included in the analysis in order to optimize treatment for this group of patients.

It can be concluded that optimal postoperative treatment of premenopausal-hormone-receptor–positive patients will remain an open issue, and the treatment of choice is inclusion in large randomized trials.

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Combined Endocrine Blockade in Premenopausal Breast Cancer: A Superior Therapeutic Option for Adjuvant Management?

To the Editor: We read with interest the results of the Austrian Breast and Colorectal Cancer Study Group Trial 5,[1] published in the December 15, 2002, issue of the *Journal of Clinical Oncology*. The authors compared adjuvant chemotherapy (CT) to adjuvant combination endocrine therapy (ET) in early-stage, premenopausal women and suggested that combined endocrine therapy (goserelin-tamoxifen) is significantly more effective in this patient population.

While the trial explores an important therapeutic issue, the authors' conclusions are perhaps overreaching. An analysis of the results shows that of the total 197 relapses in both arms (88 in the ET arm; 109 in the CT arm), there were nine more contralateral breast cancer cases in the chemotherapy arm (12 in the CT arm versus three in the ET arm). There is likely a chemo-preventive element of tamoxifen[2,3] at work, which may be responsible for this reduction of contralateral breast tumors observed in the ET arm rather than a systemic treatment effect of the ET combination. If this were taken into account, we wonder whether the statistical difference in the number of relapses observed in the two arms (88-ET; 109-CT) would remain significant, as noted in the study at present ($P = .03$).

To this end, it may also be noted that neither the overall survival rates nor the numbers of distant relapses observed in both treatment arms were statistically different. Therefore, if patients receiving chemotherapy in this trial were also to have received tamoxifen (the use of which is now an accepted standard practice in similar patient populations at the conclusion of adjuvant chemotherapy), we wonder whether the trial results would have been the same as observed. In this light, one could surmise that this study demonstrates that combination ET is perhaps as efficacious as but not superior to adjuvant chemotherapy in this patient subset. The results of this trial, however, do provide encouraging support for the premise that combination ET is a reasonable therapeutic option for systemic adjuvant treatment in patients unable to undergo adjuvant chemotherapy for some reason. This may need confirmation in future trials.

Finally, it is interesting to note that among patients in this study receiving 5 years of treatment with tamoxifen, not a single hypercoagulable event was observed. This is in variance with several previous trial results, which have noted a mild elevation in the thrombotic-event risk in patients treated with tamoxifen for prolonged time periods.[2,3]

We therefore applaud the efforts of the study group in designing an important trial, but we question the authors' conclusion of superiority of the combination ET.

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In Reply: I am offering this letter in response to the letter titled "Paradigm Shift in Adjuvant Treatment of Receptor-Positive Premenopausal Breast Cancer Patients? Not Yet!" from Drs M. Samur and H. S. Bozuck. In their letter, Drs Samur and Bozcuk raise excellent points about the lessons that may be drawn from the trials of Jonat and Jakesz. Of course, in the time since Jonat and Jakesz studies were designed, it has been shown that several chemotherapy combinations are superior to cyclophosphamide, methotrexate, and fluorouracil (CMF), or to CMF equivalents, such as doxorubicin and cyclophosphamide (AC). These chemotherapy combinations include cyclophosphamide, epirubicin, and fluorou-

racil[1]; AC and paclitaxel[2]; and perhaps dose-dense AC and paclitaxel or A, followed by T, followed by C.[3] Of course, these treatments have not, as yet, been compared with hormonal therapy in conjunction with either ovarian ablation alone, or with ovarian ablation plus tamoxifen or an aromatase inhibitor.

One might nonetheless wish to make the paradigm shift to assume that for premenopausal-hormone–receptor women, it is hormone therapy that should be considered the core treatment with or without the addition of chemotherapy, rather than chemotherapy being the core treatment with or without the addition of hormone therapy.

In light of this, many women with hormone-receptor–positive breast cancer, at low to moderate risk of recurrence, may be best treated with endocrine therapy alone. Future studies should then examine the incremental benefit risk of chemotherapy added to the core of endocrine treatment.

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In Reply: Thank you for giving us the opportunity to respond to the letters relating to the Zoladex Early Breast Cancer Research Association (ZEBRA) trial comparing goserelin (Zoladex; AstraZeneca, Macclesfield, United Kingdom) with cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy in premenopausal patients with early breast cancer.

First, in response to the comments by Drs Samur and Bozcuk, the conclusion of the ZEBRA trial is that goserelin offers an effective alternative to CMF chemotherapy — these are the findings of the trial. From the evidence available to date, it is not absolutely clear that anthracycline-containing regimens demonstrate superiority over CMF in estrogen-receptor– (ER-) positive premenopausal patients; trials to assess the relative merits of different regimens in this patient population are needed.

With respect to the comments by Dr Malayeri, we agree with the author that during recent years, it has become recognized that overexpression of *neu*/*erb*B-2 is associated with poor prognosis and a possible decrease in response to both chemotherapy and endocrine therapy. Had this information been available when the ZEBRA trial began in 1990, measurement of *neu*/*erb*B-2 expression would undoubtedly have been considered.

The ZEBRA trial was a large randomized study, and the treatment groups (goserelin 3.6 mg *v* CMF) were similar with respect to patient characteristics, primary tumor characteristics, and local therapy or radiotherapy. We therefore believe it unlikely that there would have been any relevant imbalance in *neu*/*erb*B-2 status between treatment groups in this study. Furthermore, for patients with ER-positive tumors (ie, 63% of patients disease-free at 5 years in both treatment groups), the results of the ZEBRA trial indicate that both goserelin and CMF are effective treatments in this patient population, with these results being consistent with previous findings for adjuvant therapies in premenopausal patients.[1,2]

In summary, although we agree that future studies should consider including analyses of predictive markers such as *neu*/*erb*B-2, we firmly believe that the results of the ZEBRA trial are robust and that goserelin is a valuable treatment option for premenopausal patients with ER-positive, node-positive disease.

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In Reply: The point of Drs Samur and Bozcuk is well taken and was often discussed during scientific meetings. The main problem is that chemotherapy was given for many years without knowledge of the steroid hormone receptors, because it was believed that in premenopausal patients, steroid hormone receptor status was not a predictive marker for adjuvant treatment.[1] Therefore, little information is available about the benefit of anthracycline- and taxane-containing regimens, especially in direct comparison to endocrine treatment.

In a trial presented by Roche et al,[2] complete endocrine blockade is superior to fluorouracil, doxorubicin, and cyclophosphamide (FAC) 50; however, this difference was not significant because of a low event-rate. Taking into account the importance of induction of amenorrhea in response to adjuvant chemotherapy, one has to consider the trial presented by Nabholtz et al.[3] Their results showed that amenorrhea was induced by FAC by about 35% and by docetaxel, doxorubicin, and cyclophosphamide by 55%, which is far lower than the rate of amenorrhea induced by cyclophosphamide, methotrexate, and fluorouracil (CMF), as presented in our article, as well as by Jonat et al.[4,5]

Therefore, it is not necessarily true that in premenopausal, receptor–positive patients, anthracycline- or taxane-containing regimens have to be superior to CMF, as shown in other patient cohorts. In order to clarify this statement and follow up on the issue of chemotherapy plus tamoxifen versus goserelin plus tamoxifen, we desperately need more well conducted clinical trials to be performed.

To answer the question of Dr Malayeri, we have analyzed Her-2/*neu* status in 568 patients in the Austrian Breast and Colorectal Cancer Study Group Trial 5.[4] We found that 12.2% of patients experienced Her-2/*neu* overexpression, and this was equally distributed between the two treatment groups. What we found and presented at the San Antonio Breast Cancer Symposium in December, 2002,[6] was that the overexpression of Her-2/*neu* was a significant indicator for poor prognosis, especially for overall survival.

Regardless whether the treatment is tamoxifen plus goserelin or CMF, patients with Her-2/*neu* overexpression have a significantly poorer outcome; however, this is a retrospective analysis of a large patient cohort. We believe that patients with overexpression of Her-2/*neu* are undertreated by either of these two therapy modalities.

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Correction to "Congestive Heart Failure After Treatment for Wilms' Tumor"

To the Editor: The method for estimating the lung dose in our article, previously published in the April 1, 2001, issue of the *Journal of Clinical Oncology*,[1] relied on addition of computerized dose data. The radiation oncologists on the National Wilms' Tumor Study Group Study Committee pointed out that two of the dose estimates in Table 2 of the published manuscript appeared very high. As a result, all of the doses of those who developed congestive heart failure and the controls were reviewed.

The result of this review was a correction of two of the 35 lung radiation dose estimates. These two changes resulted in minor changes in the relative risk estimates in the multiple regression analysis models in Tables 3 and 4 of the published manuscript.

The revised risk for girls was estimated to be approximately four times that for boys with the same level of cumulative doxorubicin exposure and of radiation to lung and left abdomen ($P = .004$). The revised risk was estimated to increase by a factor of 3.2 for each additional 100 mg/m^2 of doxorubicin among patients of the same sex who received the same level of cumulative radiation to the lungs and abdomen ($P < .001$). The revised risk

Table 2. Characteristics of 35 Patients Who Developed Congestive Heart Failure

Cohort	Study	Sex	Age at WT	Age at CHF	Doxorubicin (mg/m^2)	Lung Radiation (Gy)	Left Abdomen Radiation (Gy)
2	1	Male	8.2	10.6	366	**39.00***	36.30
2	1	Female	3.8	5.7	353	39.60*	0
2	1	Male	3.2	8.2	181	49.00	31.70
2	1	Female	3.9	8.8	59	13.20	35.00
2	1	Male	2.0	21.8	410	0	28.00
2	1	Female	3.3	21.0	350	**18.25***	34.40
2	1	Female	3.3	5.3	430	12.00	40.00
1	1	Female	5.3	14.7	383	14.40	36.80
1	1	Male	8.6	10.3	287	12.00	37.40
1	2	Female	1.2	21.1	299	0	24.00
1	2	Male	3.1	14.8	302	0	34.00
1	2	Female	3.9	5.3	296	12.00	30.00
1	2	Male	2.0	3.7	301	0	28.00
1	2	Female	4.0	20.6	279	0	28.50
2	2	Female	6.2	9.3	247	0	40.00
1	2	Female	3.3	20.1	429	15.00	39.70
1	2	Female	6.1	16.1	642	0	40.00
2	2	Male	2.3	4.0	521	14.00	18.00
1	2	Female	6.4	7.2	240	0	0
1	2	Female	2.3	13.8	239	12.00	30.00
1	3	Female	1.1	2.4	197	0	10.80
1	3	Male	7.2	16.1	403	11.70	0
1	3	Female	2.6	4.3	292	12.00	30.00
2	3	Female	4.1	13.8	288	12.00	0
1	3	Male	2.5	12.2	243	12.60	19.80
1	3	Female	8.2	19.4	264	12.00	19.50
1	3	Female	0.8	5.2	199	0	0
2	3	Female	10.2	12.7	427	0	0
1	3	Female	10.4	20.1	358	0	10.50
1	3	Male	7.8	11.5	691	0	0
2	3	Female	4.0	6.4	350	12.00	0
1	4	Female	3.7	5.2	301	12.00	12.00
1	4	Female	0.8	2.8	423	0	0
1	4	Female	1.3	3.0	485	0	16.20
1	4	Female	7.5	13.8	303	0	37.80

NOTE. Data in bold have been adjusted from original data in Green et al.[1]

Abbreviations: WT, Wilms Tumor; CHF, congestive heart failure.

*Recorded dose is the total resulting from overlapping fields and "boost" doses given over time in two or more radiation therapy courses after relapse(s).

Table 3. Results of the Nested Case-Control Study Multiple Regression Analysis of Continuous Treatment Variables With Stratification by Cohort

Variable	Relative Risk	95% CI	*P*
Sex, Female *v* Male	4.5	1.6 to **12.6**	.004
Doxorubicin, 100 mg/m^2	**3.2**	1.8 to **5.7**	< .001
Lung radiation, 10 Gy	1.6	1.0 to **2.5**	**.062**
Left abdomen radiation, 10 Gy	1.8	**1.2** to **2.8**	**.010**
Right abdomen radiation, 10 Gy	**0.95**	**0.68** to 1.3	**.770**

Table 4. Results of the Nested Case-Control Study Multiple Regression Analysis of Categorical Treatment Variables With Stratification by Cohort

Variable	No. of Cases	No. of Controls*	Relative Risk	95% CI	*P*
Sex					
Male	10	76	1.0	—	—
Female	25	67	**3.7**	1.4 to **9.3**	**.006**
Doxorubicin					
1-199 mg/m^2	4	36	1.0	—	—
200-299 mg/m^2	11	71	**1.0**	**0.2** to **4.2**	**.96**
≥ 300 mg/m^2	20	36	**5.0**	**1.3** to **19**	**.02**†
Lung radiation					
0	16	84	1.0	—	—
10.00-19.99 Gy	**16**	51	**1.6**	0.6 to **4.1**	**.31**
≥ 20 Gy	**3**	8	**3.1**	**0.5** to **19**	**.21**‡
Abdominal radiation					
None or right	9	**72**	1.0	—	—
Left	**26**	**71**	**3.5**	**1.2** to **10**	**.02**

NOTE. Data in bold have been adjusted from original data in Green et al.[1]

*The controls selected for two or three risk sets are doubly or triply counted.

†*P* value for trend = **.003**.

‡*P* value for trend = **.18**.

of congestive heart failure was estimated to increase by a factor of 1.6 for every 10 Gy of lung irradiation, and by 1.8 for every 10 Gy of left abdominal irradiation. By contrast, there was no evidence that right abdominal radiation increased the risk ($P = .77$).

The revised results for the categorical variable analysis demonstrated a clear trend of increasing risk with increasing doses of doxorubicin above 300 mg/m^2 and with increasing lung radiation. Patients who received left or whole abdomen radiation had a higher risk of congestive heart failure than did patients who received either no radiation therapy or radiation therapy only to the right abdomen (related risk, 3.5; $P = .02$).

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