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.

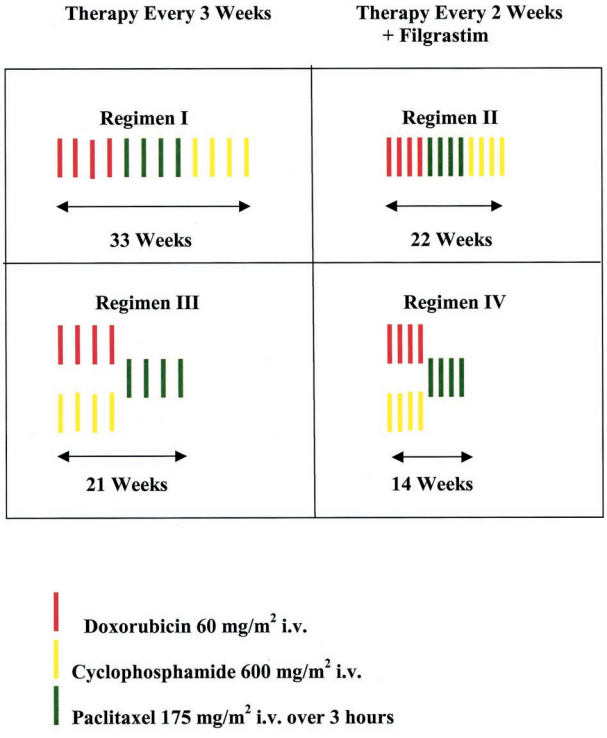

Fig 1. Treatment schema.

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,

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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 show the relation between OS and density and OS and sequence, respectively. Figure 4B shows the lack of interaction between the two factors.

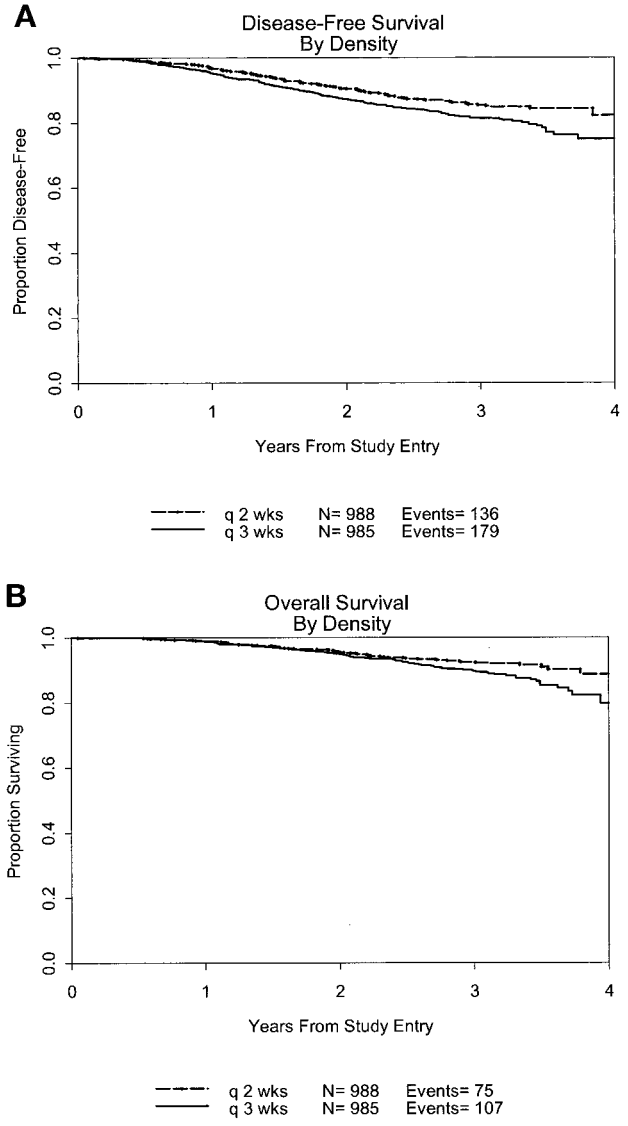

Fig 2. (A) Disease-free survival by dose density; (B) overall survival by dose density.

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 ($P <$

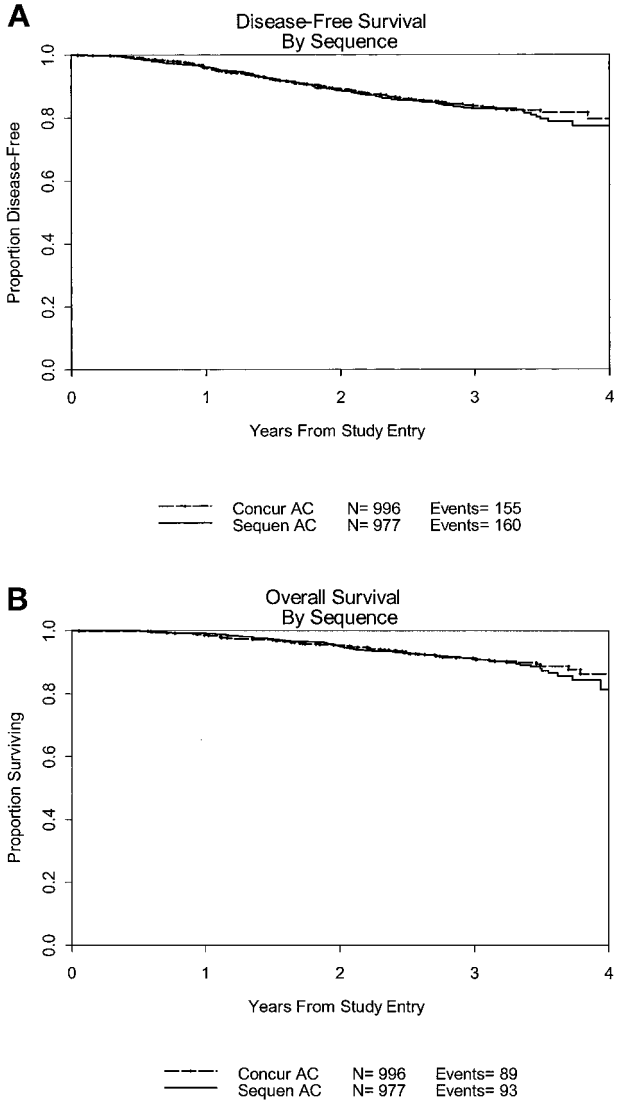

Fig 3. (A) Disease-free survival by sequence; (B) overall survival by sequence.

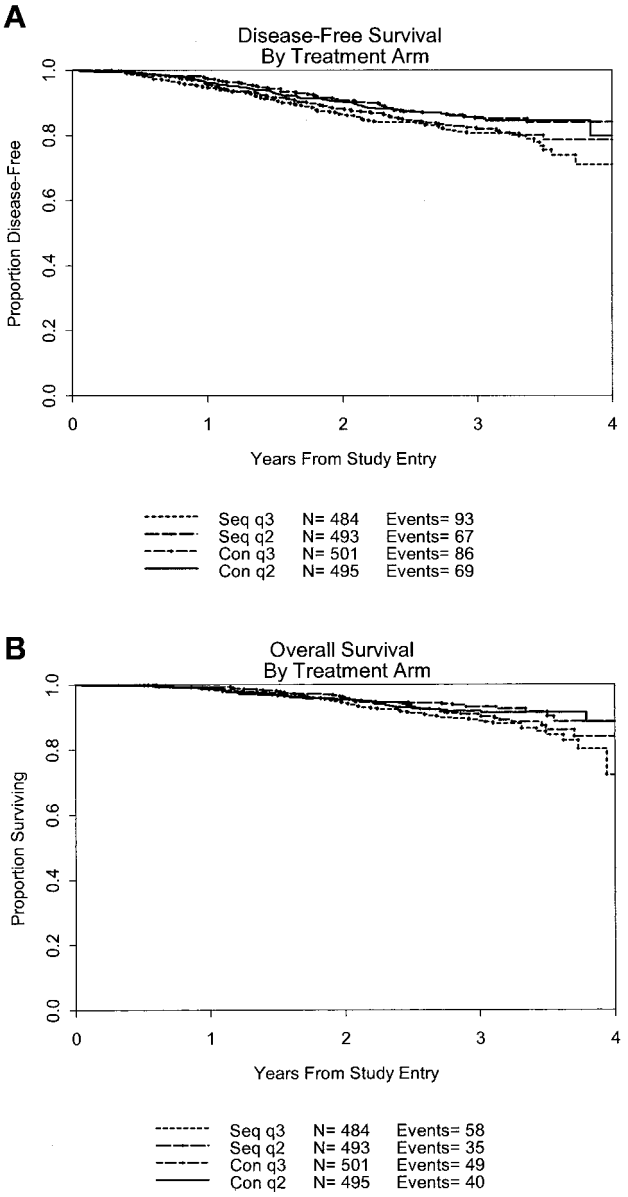

Fig 4. (A) Disease-free survival by treatment arm; (B) overall survival by treatment arm.

.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	Arm 1 (A → T → C q 3 weeks) n	Arm 1 %	Arm 2 (A → T → C q 2 weeks) n	Arm 2 %	Arm 3 (AC → T q 3 weeks) n	Arm 3 %	Arm 4 (AC → T q 2 weeks) n	Arm 4 %
	Treatment Arm							
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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DOI: 10.1200/JCO.2003.99.029

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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Current Oncology

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Article

Efficacy and Safety of Dose-Dense Chemotherapy in Breast Cancer: Real Clinical Data and Literature Review

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Simple Summary

Breast cancer treatment varies based on tumor characteristics and recurrence risk. Dose-dense chemotherapy is a strategy that shortens the interval between chemotherapy cycles to improve outcomes. This study evaluated real-world data from 80 breast cancer patients treated with this method. The results showed that patients with triple-negative breast cancer responded particularly well, with a high rate of complete tumor disappearance. Common adverse events included fatigue, reduced blood counts, and nerve-related symptoms, which were mostly manageable. However, a few patients experienced more serious complications such as pneumonia or low platelet levels. Over 80% of patients completed the treatment as planned. Based on the results of this study, dose-dense chemotherapy may offer significant benefits for patients with high-risk or aggressive breast cancer. These findings support its use in carefully selected cases and may contribute to more personalized and effective treatment strategies in early breast cancer care.

Abstract

Dose-dense chemotherapy shortens the interval between chemotherapy cycles and has shown improved outcomes in high-risk breast cancer patients. We retrospectively evaluated the efficacy and safety of dose-dense chemotherapy in 80 breast cancer patients treated at our hospital from 2020 to 2024. The regimen included epirubicin and cyclophosphamide followed by paclitaxel or docetaxel, with pegfilgrastim support. The overall treatment completion rate was 82.5%. Of the 80 patients, 55 underwent neoadjuvant chemotherapy, and the pathological complete response rate was significantly higher in triple-negative breast cancer (59.1%) compared to that in luminal-type cancer (9.1%). Common adverse events included anemia, liver dysfunction, myalgia, and peripheral neuropathy. Febrile neutropenia occurred in 8.8% of patients, with some cases linked to pegfilgrastim body pod use, particularly in individuals with low subcutaneous fat. Notably, two patients developed pneumocystis pneumonia, potentially associated with steroid administration. Despite these toxicities, most were manageable and resolved after treatment. Our findings support the efficacy of dose-dense chemotherapy, particularly in triple-negative breast cancer, while highlighting the importance of individualized supportive care and vigilance regarding hematologic and infectious complications.

Keywords: dose-dense chemotherapy; early breast cancer; neoadjuvant chemotherapy

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1. Introduction

Breast cancer has been shown to have distinct characteristics in terms of recurrence and prognosis depending on its subtype. Morgan E et al. reported in a review of studies involving 280,000 breast cancer patients that regardless of the follow-up period, hormone-receptor-negative patients had a higher risk of recurrence than hormone-receptor-positive patients [1]. In particular, triple-negative breast cancer (TNBC), which is estrogen receptor (ER)-negative, progesterone receptor (PgR)-negative and human epidermal growth factor receptor 2 (HER2)-negative, has been reported to have higher rates of recurrence and mortality compared to those in other types [2,3]. There is a peak in distant metastasis within three years of diagnosis, and the mortality rate within five years is high [3]. Additionally, in TNBC and HER2-positive breast cancer, where a pathological complete response (pCR) was achieved with neoadjuvant chemotherapy, it has been reported that the disease-free survival (DFS) and overall survival (OS) rates were significantly improved compared to those in the group that did not achieve a pCR [2,4].

Therefore, in neoadjuvant chemotherapy (NAC), a regimen with high pCR rates is being considered. Dose-dense chemotherapy is a treatment strategy that reduces the interval between doses of chemotherapy drugs to inhibit tumor cell repopulation and improve therapeutic efficacy. In breast cancer, dose-dense chemotherapy given every 2 weeks has been reported to increase the pCR rate after neoadjuvant chemotherapy compared to that under standard chemotherapy given every 3 weeks [5]. Furthermore, this method has also been shown to improve the DFS and OS. The Cancer and Leukemia Group B 9741 (CALGB9741) trial showed that the 3-year DFS was 82% in a dose-dense chemotherapy group and 75% in the standard therapy group, and the 3-year OS was 92% vs. 90%, where both were statistically superior in the dose-dense chemotherapy group. In particular, this effect was more pronounced in premenopausal patients [6]. In the PANTHER trial, the 10-year breast-cancer-recurrence-free survival was improved with dose-dense chemotherapy compared to that under the 3-week regimen. A significant benefit was seen in luminal (HR: 0.83) and HER2-positive (HR: 0.53) subgroups but not in triple-negative breast cancer (HR: 1.02) [7].

Filho OM et al. reported that dose-dense chemotherapy improved the DFS in any subtype by 23% (hazard ratio (HR): 0.77) and the OS by 20% (HR: 0.80) compared to that under standard chemotherapy given every 3 weeks; the benefits of dose-dense therapy were seen for ER+ and ER-negative subsets, without a significant interaction between the treatment arm and ER status [8].

Although dose-dense chemotherapy increases adverse events, such as neutropenia, anemia, and fatigue, compared to standard chemotherapy, neutropenia can be prevented using granulocyte-colony stimulating factor (G-CSF) every 2 weeks in dose-dense chemotherapy, and other adverse events are within the acceptable range [5–17]. Pegfilgrastim was needed as the G-CSF.

In this study, we evaluated the efficacy and safety of dose-dense chemotherapy based on actual clinical data on dose-dense chemotherapy administered at our hospital and compared them with the existing literature.

2. Materials and Methods

Eighty breast cancer patients who received dose-dense chemotherapy at our institution over a 5-year period from January 2020 to December 2024 were included in this study. The treatment regimen consisted of four doses of epirubicin and cyclophosphamide (dose-dense EC) followed by four doses of paclitaxel (dose-dense paclitaxel) every two weeks, with pegfilgrastim as the G-CSF. For alcohol-intolerant patients, paclitaxel was replaced with docetaxel every 3 weeks as the taxane drug.

The single dose of dose-dense EC therapy was 90 mg/m^2 of epirubicin and 600 mg/m^2 of cyclophosphamide. Dose-dense paclitaxel was administered at a single dose of 175 mg/m^2. Pegfilgrastim was used in combination with either a body pod or subcutaneous injection. A 3.6 mg body pod was applied on the day of treatment, and the drug was automatically injected subcutaneously 27 h later. A 3.6 mg subcutaneous injection was administered on the second or third day of treatment, with the drug administered subcutaneously.

The efficacy and safety of dose-dense chemotherapy were evaluated retrospectively, and pathologic effects were also analyzed in addition in the NAC group. A pathological complete response was defined as the disappearance of the invasive carcinoma, even if an intraductal component remained. CTCAE 5.0 was used to evaluate adverse events, and the Kaplan–Meier survival curve and Fisher's exact probability test were used for the statistical analysis. For cases in which docetaxel was used from the outset due to alcohol intolerance, only dose-dense EC therapy was evaluated in this study.

3. Results

The patients' background is shown in Table 1. The age of the patients was 30~78 years (mean: 56.7 years), and the observation period was 3~64 months (median: 38 months). The subtypes were a triple-negative type (TNBC) in 30 cases and a luminal type (luminal) in 50 cases; HER2-positive cases were not included. Fifty-three patients (66.3%) were axillary-lymph-node-positive cases at the time of diagnosis, with clinical stage I in 15 cases, stage II in 46 cases, and stage III in 19 cases. A total of 75 cases were invasive ductal carcinoma of the breast, 4 cases were invasive lobular carcinoma, and 1 case was invasive micropapillary carcinoma.

Table 1. Patients' characteristics.

	Premenopause 27 (33.8%)	**Postmenopause 53 (66.3%)**	**Total 80 (100%)**
Median age (range)	44.1 (30–50)	63.0 (46–78)	56.7 (30–78)
Observation period (months)	35 (9–52)	40 (3–61)	38 (3–64)
Menopausal status			
Premenopausal	25	0	25 (31.2%)
Postmenopausal	0	51	51 (63.8%)
Unknown *[1]	2	2	4 (5.0%)
Histopathological type			
Invasive ductal carcinoma	25	50	75 (93.8%)
Invasive lobular carcinoma	2	2	4 (5.0%)
Other	0	1	1 (1.3%)
Clinical stage (before chemotherapy)			
I	4	11	15 (18.8%)
II	16	30	46 (57.5%)
III	7	12	19 (23.8%)
Tumor stage (before chemotherapy)			
T1	6	18	24 (30.0%)
T2	15	21	36 (45.0%)
T3	3	4	7 (8.8%)
T4	3	10	13 (16.3%)
Tumor grade (before chemotherapy)			
1	12	16	28 (35.0%)
2	10	24	34 (42.5%)
3	5	13	18 (22.5%)
Hormone receptor			
ER and/or PgR: positive	20	30	50 (62.5%)
ER and PgR: negative	7	23	30 (37.5%)

Table 1. *Cont.*

	Premenopause 27 (33.8%)	Postmenopause 53 (66.3%)	Total 80 (100%)
HER2			
positive	0	0	0
negative	27	53	80 (100%)
Ki67			
≤20	15	20	35 (43.8%)
>20	12	33	45 (56.3%)
Subtype			
Luminal	20	30	50 (62.5%)
Triple-negative	7	23	30 (37.5%)
HER2	0	0	0
Axillary lymph node status (at the diagnosis) *2			
Positive	16	37	53 (66.3%)
Negative	11	16	27 (33.8%)
No. of positive nodes (post-surgery)			
0	7	33	40 (50.0%)
1–3	13	13	26 (32.5%)
4–9	5	6	11 (13.8%)
≥10	2	1	3 (3.8%)
Chemotherapy			
Neoadjuvant	19	36	55 (68.8%)
Post-operative	8	17	25 (31.3%)
Pathological therapeutic effect after NAC (n = 55)			
pCR	5	11	16
Non-pCR	14	25	39
Post-chemotherapy			
Endocrine	20	30	50 (62.5%)
CDK4/6 inhibitor	5	9	14 (17.5%)
Event			
Distant recurrence	0	5	5 (6.3%)
Death	0	3	3 (3.8%)

*1 For simplicity, the following classification was used. Premenopausal: 50 years old or younger; postmenopausal: older than 50 years; *2 p = 0.004, odds ratio: 4.71 (95% CI: 1.69–13.13), hazard ratio of 1.96 (95% CI: 1.30–2.96); ER: estrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor2; NAC: neoadjuvant chemotherapy; pCR: pathological complete response.

There were 27 premenopausal patients, and there were 53 postmenopausal patients.

When stratified by menopausal status, the postmenopausal group showed a significantly higher rate of pathologically node-negative disease after surgery compared with that in the premenopausal group (62.3% vs. 25.9%; Fisher's exact p = 0.004; OR for ≥1 positive node in pre- vs. postmenopausal patients: 4.71; 95% CI: 1.69–13.13). Trends toward a lower hormone-receptor-positive rate, a higher Ki-67 index, and a higher proportion of triple-negative tumors were observed in the postmenopausal patients; however, these did not reach statistical significance (all $p > 0.05$). The pathologic complete response rates among patients receiving neoadjuvant chemotherapy were similar between groups (26.3% vs. 30.6%; p = 1.00).

Of the 55 patients who received NAC, 22 had TNBC and 33 had luminal-type cancer (Table 2). The overall pCR rates were 29.1% (16/55) and 59.1% (13/22) in the TNBC group and 9.1% (3/33) in the luminal group. The results of the Fisher's test showed that the pCR rate in the TNBC group was statistically significantly higher than that in the luminal group (odds ratio: 14.4, p = 0.0001).

Table 2. Comparison of NAC effects by subtype.

	Triple-Negative Type (*n* = 22)	Luminal Type (*n* = 33)
Clinical chemotherapy effect, no (%)		
cCR	11 (50.0)	5 (15.1)
cPR	11 (50.0)	27 (81.8)
cSD	0 (0)	1 (3.0)
cPD	0 (0)	0 (0)
Pathological chemotherapy effect, no (%) *		
pCR	13 (59.1) *	3 (9.1) *
non-pCR	9 (40.9)	30 (90.9)

* Odds ratio (OR): 14.4, *p*-value: 0.0001; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; c: clinical; *p*: pathological.

The eight cases of TNBC who did not undergo NAC were those who were considered to have non-invasive carcinoma preoperatively but were found to have invasion on postoperative pathology or those who preferred to proceed with surgery because of the COVID-19 situation. Around 2020, there were cases where surgeries were postponed due to COVID-19 infections among medical staff, patients, and their families. As a result, some patients requested to undergo surgery as early as possible. They were concerned that their surgeries might be canceled due to COVID-19.

We investigated the differences in the pCR rates after NAC between TNBC and the luminal type in premenopausal and postmenopausal patients (Figure 1).

	premenopousal *n*=27	postmenopausal *n*=53	total *n*=80
TNBC	7	23	30
Luminal	20	30	50
HER2	0	0	0

NAC

		premenopousal *n*=19	postmenopausal *n*=36	total *n*=55
TNBC *n*=22	pCR	4	9	13(23.6%)
	non-pCR	2	7	9(16.4%)
Luminal *n*=33	pCR	2	1	3(5.5%)
	non-pCR	11	19	30(55.5%)

Post Operation Chemotherapy

	premenopousal *n*=8	postmenopausal *n*=17
TNBC	1	7
Luminal	7	10

Figure 1. Classification based on menopausal status.

However, no significant differences in treatment efficacy were observed between the premenopausal and postmenopausal patients across subtypes. When comparing TNBC before and after menopause using Fisher's exact probability test (two groups × 2), the following results were yielded: $p = 1.00$ (two-tailed), odds ratio (pre/post) = 1.56 (95% CI: 0.22–11.09), and risk ratio (RR) = 1.19 (95% CI: 0.58–2.42). When limited to luminal-type cancer, $p = 0.55$, OR = 3.45, and RR= 3.08 (95% CI: 0.31–30.59). For pre- and postmenopausal women with a mixed subtype, $p = 0.77$, and OR = 1.20 (95% CI: 0.36–4.03). In either case, no results were obtained indicating that premenopause was statistically advantageous over postmenopause. As shown in Table 2, the only finding was that TNBC had a better treatment response than that for the luminal type, regardless of menopausal status.

In either case, no results were obtained indicating that premenopause was statistically advantageous over postmenopause.

The Kaplan–Meier curves for the DFS are shown (Figure 2). The number of recurrence events was only five cases in the postmenopausal group, and there was no recurrence in the premenopausal group, and no significant difference was observed. There were only three deaths after menopause, and no trend was observed before or after menopause.

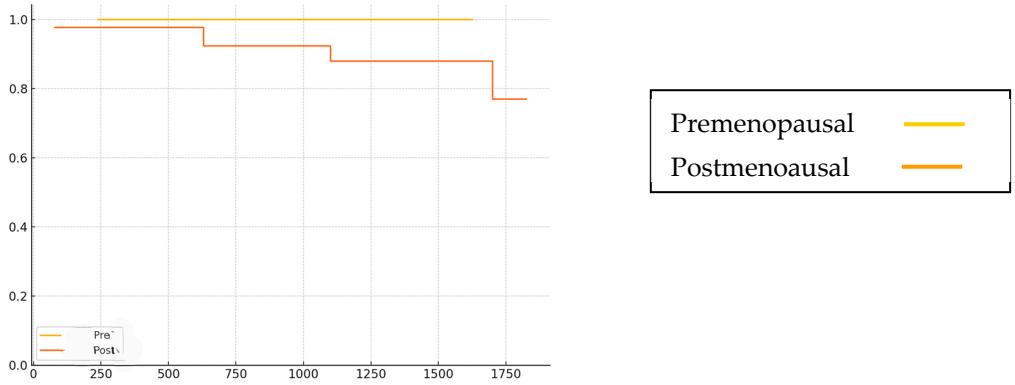

Figure 2. DFS in pre- and postmenopausal patients.

The treatment completion rate was 82.5% (66/80), and 14 patients (17.5%) could not continue dose-dense chemotherapy due to adverse events. The main adverse events are shown in Table 3.

Hematologic adverse events, such as liver dysfunction (58.8%) and anemia (57.6%), were observed in more than half of the patients, but most were Grade 1 or 2. Thrombocytopenia was observed in 22.6% of patients, and leukopenia and neutropenia were observed in 18.8% of patients. Febrile neutropenia was observed in seven patients (8.8%).

Non-hematologic complications included alopecia (100%), myalgia (70.1%), arthralgia (57.6%), and peripheral neuropathy (55.0%), which were observed in more than half of the patients. In addition, fatigue (43.8%), nausea (37.6%), and anorexia (27.6%) were also common.

Grade 3 or higher adverse events included leukopenia and neutropenia at 11.3%, febrile neutropenia at 8.8%, and thrombocytopenia at 1.3%. Non-hematologic adverse events included pneumonia at 5.0% and fatigue at 2.5%, while anorexia, nausea, arthralgia, and myalgia were each experienced in 1.3%. Among these, Grade 4 events consisted of leukopenia (5.0%), neutropenia (5.0%), and thrombocytopenia (5.0%). The reasons for discontinuation were Grade 3/4 anemia and neutropenia, drug-induced pneumonia, pneumocystis pneumonia, liver dysfunction, and Grade 4 thrombocytopenia due to pegfilgrastim.

Two of the patients who discontinued treatment were diagnosed with pneumocystis pneumonia, which needed to be distinguished from COVID-19-associated pneumonia. Due to severe pneumonia, oxygen administration and hospitalization for more than two weeks were required. After discharge, continued chemotherapy became difficult due to a decline in performance status, so chemotherapy was not continued, and surgery was performed.

One patient diagnosed with thrombocytopenia due to pegfilgrastim was treated with a pegfilgrastim body pod in the first instance, and Grade 4 neutropenia and thrombocytopenia developed on day 8. Antibiotic therapy was administered for febrile neutropenia, and their platelet counts decreased to 23,000/mm^3, but no blood transfusion was given because the patient refused. The patient was kept under observation, and improvement to Grade 1 was observed by day 15. We also switched to subcutaneous injection of pegfilgrastim for this patient and reduced the dose of chemotherapy. Neutropenia improved, but throm-

bocytopenia similarly decreased to Grade 4. Considering thrombocytopenia associated with pegfilgrastim, we switched to a 3-week regimen without pegfilgrastim. This means that dose-dense chemotherapy was discontinued. After this change, thrombocytopenia remained at Grade 1. In our institution, several thin women with low subcutaneous fat who received a pegfilgrastim body pod developed Grade 4 febrile neutropenia. We switched to subcutaneous injections of pegfilgrastim, and Grade 4 neutropenia no longer occurred.

Table 3. Adverse events.

	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia (18.8%)	6 (7.5)	0 (0)	5 (6.3)	4 (5.0)
Neutropenia (18.8%)	5 (6.2)	1 (1.3)	5 (6.3)	4 (5.0)
Febrile neutropenia (8.8%)	0 (0)	0 (0)	7 (8.8)	0 (0)
Anemia (57.6%)	33 (41.3)	10 (12.5)	3 (3.8)	0 (0)
Thrombocytopenia (22.6%)	16 (20.0)	1 (1.3)	0 (0)	1 (1.3)
aspartate aminotransferase (58.8%)	40 (50.0)	6 (7.5)	1(1.3)	0 (0)
Anorexia (27.6%)	20 (25.0)	1 (1.3)	1 (1.3)	0 (0)
Nausea (37.6%)	24 (30.0)	5 (6.3)	1 (1.3)	0 (0)
Constipation (25.1%)	15 (18.8)	5 (6.3)	0 (0)	0 (0)
Diarrhea (3.8%)	3 (3.8)	0 (0)	0 (0)	0 (0)
Fatigue (43.8%)	29 (36.3)	4 (5.0)	2 (2.5)	0 (0)
Arthralgia (57.6%)	40 (50.0)	5 (6.3)	1 (1.3)	0 (0)
Myalgia (70.1%)	50 (62.5)	5 (6.3)	1 (1.3)	0 (0)
Peripheral neuropathy (55.0%)	34 (42.5)	10 (12.5)	0 (0)	0 (0)
Edema (16.3%)	10 (12.5)	3 (3.8)	0 (0)	0 (0)
Eczema (8.8%)	7 (8.8)	0 (0)	0 (0)	0 (0)
Stomatitis (10.1%)	7 (8.8)	1 (1.3)	0 (0)	0 (0)
Lung infection (7.5%)	0 (0)	2 (2.5)	4 (5.0)	0 (0)
Fever (12.5%)	8 (10.0)	2 (2.5)	0 (0)	0 (0)
Dysgeusia (17.5%)	12 (15.0)	2 (2.5)	0 (0)	0 (0)
Facial nerve disorder (1.3%)	0 (0)	1 (1.3)	0 (0)	0 (0)
Headache (3.8%)	3 (3.8)	0 (0)	0 (0)	0 (0)
Alopecia (100%)	0 (0)	80 (100.0)	0 (0)	0 (0)

Other adverse events, such as liver dysfunction, myalgia/arthralgia, peripheral neuropathy, fatigue/malaise, and alopecia, occurred, with most cases showing symptomatic improvements after chemotherapy was completed.

There were three cases of distant recurrence (3.8%), including one case of inflammatory breast carcinoma with TNBC in whom a pCR was obtained through NAC. Two months after surgery, multiple liver metastases were found, and the breast carcinoma was PD-L1-positive. Chemotherapy with an immune checkpoint inhibitor was ineffective, and the patient died four months after surgery. The other two patients had luminal-type carcinoma with lymph node metastasis. Both patients had a non-pCR after neoadjuvant chemotherapy and died two years later due to liver and lung metastases, respectively.

4. Discussion

Dose-dense chemotherapy, characterized by standard-dose agents administered at shortened intervals with G-CSF support, has been shown to improve the disease control in patients with high-risk early breast cancer [2,4,6,8]. The CALGB9741 trial demonstrated significant survival benefits, including a 7% absolute improvement in the 3-year DFS and a 2% improvement in the OS, with pronounced efficacy in premenopausal women [6]. Several subsequent randomized trials and meta-analyses, including those by Venturini, Del Mastro, and Zhou, have confirmed these findings, establishing dose-dense chemotherapy as a standard strategy in selected populations [5–17]. In particular, Fornier M et al. reported in their review that dose-dense chemotherapy is expected to be particularly effective in triple-negative breast cancer and high-risk premenopausal patients [11]. Furthermore, dose-dense chemotherapy has been reported to improve the DFS and OS compared to those under chemotherapy every three weeks, even in ER-positive triple-negative breast cancer [8].

In our study, too, the TNBC group was more likely to obtain a pCR, with a significant difference of 59% compared to that in the luminal group, which had a pCR rate of 6%. This result supports the high efficacy of dose-dense chemotherapy in TNBC. Although the number of cases was limited, the pCR rate for TNBC patients in this study was 59.1%, which is higher than the pCR rates shown in other clinical trials (32.7–52%) [2,5]. On the other hand, the pCR rate for the luminal type was low at 9.1%, suggesting that the efficacy of dose-dense chemotherapy in luminal-type cancer is limited.

Previous reports have indicated that in TNBC, the presence of insulin-like growth factor II mRNA-binding protein 3 (IMP3) expression is associated with a poor response to chemotherapy [18]. However, in recent regimens, including dose-dense chemotherapy, there has been no difference in the efficacy of preoperative chemotherapy based on the presence or absence of IMP3 expression, and dose-dense chemotherapy is considered effective, even for more aggressive TNBC unresponsive to previous regimens [19].

Adverse events were observed in many cases in the above clinical trials, similar to those seen with conventional chemotherapy. The 2022 Japanese Guidelines for the Management of Breast Cancer provide a literature review of the adverse events associated with dose-dense chemotherapy [20]. Anemia was analyzed in two randomized controlled trials (RCTs) involving 4172 patients. In all grades, the incidence of the development of Grade 1 anemia or higher during treatment was 37.1% in the control group who underwent dose-dense chemotherapy, with approximately 34.5% reaching Grade 3 and 37.9% requiring a blood transfusion. Based on these findings, it is considered necessary to carefully monitor blood sampling data [20–22].

In our hospital, anemia during dose-dense chemotherapy improved naturally in all cases upon the completion of chemotherapy. In the above Japanese guidelines for the treatment of breast cancer, the evaluation of febrile neutropenia was analyzed in one RCT involving 2155 participants. The risk was reduced in the dose-dense chemotherapy group (1.4%) compared to that in the control group (3.6%) (risk difference: −0.02; 95% CI: −0.03 to −0.01) [20]. This result was considered necessary due to the mandatory use of pegfilgrastim.

The incidence of adverse events was similar in our study, but febrile neutropenia was observed in 8.8% of cases (7/80). They required antibiotic treatment and hospitalization. At our institution, febrile neutropenia occurred primarily after the first administration, and although the number of cases was small, it was observed in several cases in women who were thin with little subcutaneous fat and who received a pegfilgrastim body pod.

In two cases of pneumocystis pneumonia, febrile neutropenia occurred when the treatment was switched from anthracycline (four instances of dose-dense EC) to taxane

(dose-dense paclitaxel). This type of pneumonia is also known as an opportunistic infection, and it was thought that the administration of steroids every two weeks to prevent adverse events may have contributed to its development. Of these, one case was reported by Yagi [23]. Pneumonia caused by Pneumocystis jirovecii pneumonia can appear to worsen despite effective treatment, and this coincided with the spread of COVID-19, making diagnosis and treatment difficult. During the treatment for Pneumocystis jirovecii pneumonia, the phenomenon of symptoms appearing to worsen despite effective treatment is known as a "paradoxical response" or "immune reconstitution inflammatory syndrome (IRIS)" [24].

In this study, Grade 4 thrombocytopenia was observed. A pegfilgrastim body pod was used in the first session of chemotherapy, and the treatment was switched to a subcutaneous injection of a pegfilgrastim formulation for the second session, both of which resulted in Grade 4 thrombocytopenia. After discontinuing pegfilgrastim due to concerns about its effects, thrombocytopenia remained at Grade 1, leading us to conclude that pegfilgrastim was the cause.

Pegfilgrastim stimulates the hematopoietic stem cells in the bone marrow to promote the production of neutrophils. It is modified using PEG (polyethylene glycol), which slows its breakdown in the body and gives it a longer duration of action [25–30]. In a dose-dense regimen, it is important to manage neutropenia, and pegfilgrastim is a drug necessary to suppress neutropenia in order for treatment to be administered every two weeks. However, patients using pegfilgrastim have a significantly higher risk of thrombocytopenia compared to that in non-users (adjusted odds ratio: 5.7; 95% confidence interval: 4.3–7.5) [31]. Additionally, an analysis comparing the adverse events between filgrastim and pegfilgrastim indicated that pegfilgrastim was associated with a higher incidence of thrombocytopenia.

Dose-dense chemotherapy has been reported to cause other adverse events, such as anemia, liver dysfunction, fatigue, muscle and joint pain, and peripheral neuropathy [1–8,12]. In this study, similar symptoms were observed, but many cases showed improvements after the completion of dose-dense chemotherapy. Regarding hair loss, our clinic does not use scalp-cooling devices, and this was approved by all patients.

Although the number of cases examined was small, our dose-dense chemotherapy showed a high pCR rate, especially in patients with TNBC. On the other hand, the limited efficacy of dose-dense chemotherapy in luminal-type cancer suggests the importance of an individualized treatment strategy.

Regarding adverse events, the treatment completion rate was 82.5%, indicating that dose-dense chemotherapy was generally well tolerated. However, it is important to note that febrile neutropenia can occur in less than 10% of cases. Some serious complications such as pneumocystis pneumonia and pegfilgrastim-induced thrombocytopenia can rarely occur. By carefully managing adverse events, dose-dense chemotherapy for early breast cancer patients with a high recurrence risk was completed in more than 80% of cases. Particularly in TNBC, it showed a high pCR rate and is considered to have promising therapeutic effects.

This study included several patients aged 70 years or older. Most were able to complete dose-dense therapy similarly to patients in other age groups; however, some elderly patients had concomitant organ dysfunction due to aging.

Yildirim et al. reported that elderly patients aged 65 years or older are more prone to Grade 3–4 adverse events than younger patients (71% vs. 46.4%, $p < 0.001$), and the pCR rate is lower than that in younger patients (26.6% vs. 33.3%, $p = 0.24$). However, in summary, it is applicable if used selectively with caution regarding its toxicity [32]. Another report states that dose-dense chemotherapy is possible even in elderly patients aged 60 years or older, with toxicity within the acceptable limits [31–33].

In high-risk early triple-negative breast cancer, the combination of pembrolizumab, an immune checkpoint inhibitor, and chemotherapy as neoadjuvant therapy has been reported to increase pCR rates (the KEYNOTE-522 study) [34]. Immune checkpoint inhibitors require caution regarding immune-related adverse events, and in facilities like ours with a high proportion of elderly patients, careful consideration is necessary when determining their appropriate use.

CDK4/6 inhibitors plus endocrine therapy is the first-line treatment for hormone receptor-positive, HER2-negative breast cancer with metastatic recurrence. Clinical trials have reported its efficacy as neoadjuvant therapy for early-stage breast cancer, but it is not covered by insurance in Japan, and results from future clinical trials are anticipated.

In this study, it was demonstrated that dose-dense chemotherapy was safe, with acceptable toxicity in a general clinical setting, although caution is required. Additionally, a higher pCR rate was observed in TNBC compared to that in luminal-type cancer. Furthermore, when comparing premenopausal and postmenopausal patients, fewer events were observed in the former, and no significant differences were found in DFS or OS.

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Abbreviations

The following abbreviations are used in this manuscript:

pCR	Pathological complete response
DFS	Disease-free survival
OS	Overall survival
EC	Epirubicin/cyclophosphamide
NAC	Neoadjuvant chemotherapy
TNBC	Triple-negative breast cancer
G-CSF	Granulocyte-colony stimulating factor
PD-L1	Programmed cell death ligand 1
IMP3	Insulin-like growth factor II mRNA-binding protein 3

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The use of granulocyte colony-stimulating factors in the management of breast cancer patients

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The dynamic development of oncology poses new challenges to health care practitioners (HCPs), related to the introduction of modern targeted therapies, immunotherapies, or new chemotherapy regimens. The previous treatment algorithm for neutropenia and febrile neutropenia have significantly reduced the frequency of these complications in long-term therapies. Currently, breast cancer (BC) treatment is also based on the use of modern therapies, showing different toxicity profile. This article discusses the role of granulocyte colony-stimulating factors (G-CSFs) in well-known and new therapies used in the treatment of breast cancer patients. The factors influencing the development of hematological complications such as neutropenia and febrile neutropenia were presented. An important aspect of the assessment of patients at increased risk of therapy-induced toxicity was discussed with highlighting the fact that the treatment regimen is not the only factor influencing the development of adverse events (AEs). The aim of the study is to consolidate recommendations for the primary and secondary prevention of neutropenia and febrile neutropenia and related improvement of treatment outcomes in patients with BC.

KEYWORDS

breast cancer, neutropenia, febrile neutropenia, granulocyte colony-stimulating factors, filgrastim, pegfilgrastim, anticancer therapy toxicity

Introduction

Breast cancer is the most frequently diagnosed malignant tumor in women. The current decrease in mortality results from early diagnosis thanks to modern screening techniques and advances in local and systemic treatment (1). However, targeted therapies, immunotherapy, chemotherapy regimens with a shortened interval between cycles are associated with a different toxicity profile. Therefore, there is a need for developing new management algorithms in everyday clinical practice. Appropriate management of adverse effects during the treatment of early and advanced BC is an important element of anticancer therapy and directly improves prognosis.

Neutropenia and febrile neutropenia

Neutropenia, defined as a decrease in the absolute number of peripheral blood neurophils <1500 G/L, is a frequent adverse effect of anticancer treatment (2). According to the European Society for Medical Oncology (ESMO), febrile neutropenia (FN), is characterized by an absolute decrease in neurophils count below 500 G/L or a predicted decrease in their number below 500 G/L with an associated increase in body temperature above 38.3°C or above 38°C in two consecutive measurements within 2 hours (2).

Ten years ago, FN occurred in up to 17% of BC patients receiving systemic therapies (3). The risk of this complication depends not only on the treatment regimen used, but also other factors. Elderly patients, especially with comorbidities, advanced disease stages and FN in medical history are at increased risk of developing this complication (4).

Appropriate assessment of patient is of significant importance in decision making process regarding G-CSF prophylaxis. The risk of FN-related complications in BC patients can be estimated using the MASCC (Multinational Association of Supportive Care in Cancer) risk index. A score of ≥ 21 is considered as low risk, with the frequency of serious complications of 6% (probability of death - 1%), and if number of points is below 21, the risk of serious complications is as high as 39% (risk of death - 14%) (5, 6).

It has been shown that patients with bacteremia have a higher risk of death related to FN. In patients with Gram-negative and Gram-positive bacteria in blood cultures, mortality increases to 18% and 5%, respectively (7). The etiology of bacteremia has additional prognostic value, especially in patients at high risk of complications (6).

Granulocyte colony-stimulating factors

Filgrastim

The first available G-CSF was a short-acting recombinant methionyl human granulocyte colony-stimulating factor filgrastim. Clinical trials evaluating its activity and safety in patients undergoing cytotoxic therapy began in 1988 (8). The dose of filgrastim is 0.5 million units (5 μg)/kg of body weight (b.w.)/day. The first dose should not be administered earlier than 24 hours after chemotherapy completion. A transient increase in neurocyte counts may usually be observed 1–2 days after therapy initiation. However, to achieve a sustained response, filgrastim should not be discontinued before the expected nadir and the neutrophil count recovery. Filgrastim should be administered approximately 10–14 days during chemotherapy with 3-week or longer cycles (9).

According to the retrospective study, the use of filgrastim reduces the risk of G3/G4 neutropenia or shortens its duration in patients undergoing chemotherapy, compared with placebo or no intervention. It significantly reduces the risk of FN and the number of FN-related hospitalizations, the use of antibiotics, and the number of deaths (10).

G-CSF has a direct impact on the effectiveness of anticancer treatment because it affects the proper course of systemic treatment over time without reducing the doses. However, none of the studies assessing the efficacy of filgrastim found its effect on prolonging overall survival (OS) or disease-free survival (DFS). The characteristic adverse effects of filgrastim were generalized bone pain and flu-like symptoms (11).

Pegfilgrastim

Given the short half-life of filgrastim and the need for daily dosing, an attempt was made to modify this molecule, resulting in a long-acting, newer-generation drug. Pegfilgrastim is a covalent conjugate of recombinant human G-CSF with one molecule of polyethylene glycol, with reduced plasma clearance and extended half-life to 80 hours. This allows for reduction of the frequency of G-CSF administration to a single dose during chemotherapy cycle while maintaining previous efficacy (6 mg per chemotherapy cycle, administered at least 24 hours after treatment cessation) (6, 12). The drug was registered by the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) in 2002 based on the results of two phase III studies. The first study assessed the efficacy and safety of pegfilgrastim compared with filgrastim in BC patients undergoing neoadjuvant chemotherapy according to AT regimen. A single dose of pegfilgrastim was as effective as 10 injections of filgrastim in reducing the risk and duration of grade 3 and 4 neutropenia. The frequency of FN during 4 cycles of chemotherapy was lower in pegfilgrastim group (9% vs. 18%) (13).

The second study compared the efficacy and safety of pegfilgrastim and filgrastim in 157 BC patients receiving combined chemotherapy with docetaxel and doxorubicin. The incidence of G4 neutropenia was similar between the two groups. FN occurred in 13% of patients receiving pegfilgrastim compared with 20% of patients receiving filgrastim (14).

In majority of the studies the use of pegfilgrastim resulted in a lower risk of neutropenia and FN. According to meta-analysis of 5 studies, including 617 patients, also with BC, a single dose of

Abbreviations: AC, doxorubicin, cyclophosphamide; BC, breast cancer; CDK4/6, cyclin-dependent kinase 4/6; CTX – cyclophosphamide; dd - dose dense; DFS - disease free survival; EBC - early breast cancer; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, Food and Drugs Administration; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; MASCC, Multinational Association of Supportive Care in Cancer; MBC, metastatic breast cancer; MTX, methotrexate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; pCR, pathological complete response; PD-L1, programmed death ligand 1; PS, performance status; QoL, quality of life; Q2W, every 2 weeks; Q3W, every 3 weeks; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TC, docetaxel, cyclophosphamide; TCH, docetaxel, carboplatin, trastuzumab; TCH+/-P, docetaxel, carboplatin, trastuzumab +/- pertuzumab.

pegfilgrastim was significantly more effective in minimizing the risk of G3/G4 neutropenia and FN compared to 14 days of filgrastim therapy (15). Similar results were obtained in Cooper et al. meta-analysis of 20 studies, including over 4,000 cancers patients undergoing systemic therapies (16, 61).

These findings are consistent with those of Li et al. (2020), who in a systematic review and meta-analysis demonstrated that PEGylated G-CSF significantly reduces the incidence of febrile neutropenia and is at least as effective, if not superior, to filgrastim in breast cancer patients receiving chemotherapy (17).

In Cornes et al. meta-analysis of 11 randomized clinical trials and 2 non-randomized studies, no significant advantage of long-acting over short-acting preparations was observed in reducing the incidence of FN (18). One of the hypotheses explaining the contradictory results is the lower efficacy of short-acting preparations resulting from a lower total dose compared to a single injection of pegfilgrastim. It is estimated that 6 mg of pegfilgrastim is equivalent to 11 filgrastim administrations (6, 18). in addition, a single injection of pegfilgrastim does not significantly reduce QoL, compared to therapy lasting at least 10 days in each chemotherapy cycle. It is important to note that, compared to filgrastim, pegfilgrastim is not compatible with a weekly chemotherapy regimen.

Primary and secondary prophylaxis

G-CSF therapy may be implemented as primary or secondary prophylaxis. The latter is introducing in patients with G3/G4 neutropenia, FN or FN-related infection during cytotoxic therapy. This prevents the occurrence of neutropenia or FN or shortens their duration. During primary prophylaxis, the patient receives G-CSF after the first course of chemotherapy due to the primary high risk of FN. It is recommended to implement primary prophylaxis in patients receiving treatment according to regimens that are associated with FN risk greater than 20%. An intermediate risk of FN, i.e., 10-20%, does not require the absolute use of G-CSF prophylaxis (Figure 1) (2, 6).

Important factors that should be taken into account include patient's age and performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) score. A significant increase in FN risk is also associated with comorbidities, such as chronic renal failure, liver failure or heart disease. The frequency of hematological complications, including FN, is significantly higher in patients receiving intensive treatment due to advanced cancer as compared to patients with early stages. However, each clinical situation should be assessed individually (2, 6).

The utility of primary G-CSF prophylaxis has also been confirmed in a recent meta-analysis by Nozawa et al. (2024), who concluded that such prophylaxis significantly reduces the risk of febrile neutropenia without compromising the safety profile in patients with invasive breast cancer (19).

Use of GCS-F during chemotherapy

The current systemic treatment of BC patients should be individualized, based on many factors, including clinical stage,

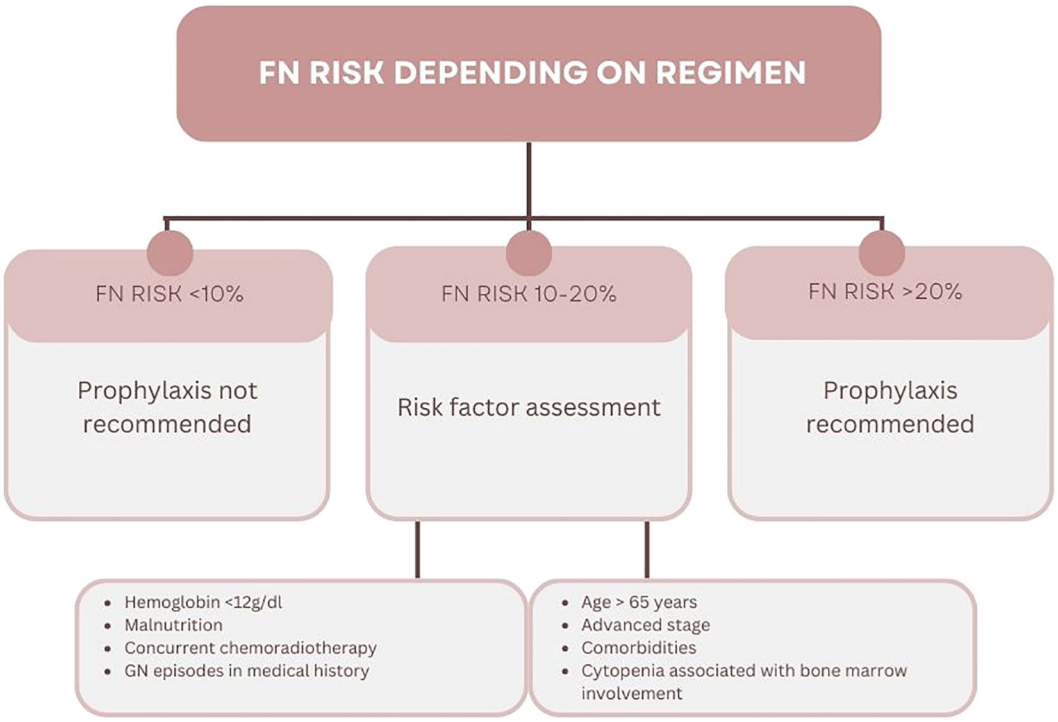

FIGURE 1
Stratification of febrile neutropenia risk groups (2, 6).

biological subtype, *BRCA* mutation status, programmed death ligand 1 (PD-L1) expression level, *PIK3Ca* mutation status and patient's general condition. However, chemotherapy is still one of the basic treatment modalities (16, 20).

In patients with triple negative and human epidermal growth factor receptor 2 [HER2] -positive early breast cancer (EBC), not achieving pathological complete response (pCR), further systemic treatment is implemented in addition to neoadjuvant therapy (18). Similarly, HR+/HER2− patients at high risk of recurrence—whether treated with neoadjuvant endocrine therapy or primarily eligible for surgery—also require adjuvant chemotherapy. Unfortunately, this prolongs the therapeutic process and increases the risk of additional toxicities. Therefore, minimizing the risk of AEs (including FN) and the resulting delays in treatment cycles and dose reductions has a significant impact on treatment of patients with EBC (21).

Chemotherapy in early breast cancer

The therapy based on anthracyclines and taxane, being a "gold standard" perioperative treatment of BC patients, is associated with 10-20% risk of FN (Table 1). Primary prophylaxis with G-CSF is therefore not recommended for all patients receiving this regimen. Currently, the standard anthracycline treatment regimen, i.e., every 3 weeks, is reserved for patients with low disease dynamics and additional disease burden. Remaining patients require intensive chemotherapy regimen (dose dense, dd), which is associated with >20% risk of FN. It was shown in the randomized clinical trial, that anthracyclines administered every 14 days (Q2W) prolonged DFS and OS compared to the conventional rhythm of therapy. The administration of G-CSF as primary prophylaxis (3–10 days between treatment cycles) was associated with the requirement to maintain 14-day therapy cycles. Dose-dense regimens were associated with a lower frequency of FN and G3/G4 neutropenia, compared to the conventional rhythm of treatment without G-CSF prophylaxis (6% vs 33%, respectively). Additionally, there were more treatment delays during the 3-week treatment regimen compared to the 2-week regimen (38% vs 15%, respectively) (22).

TABLE 1 The risk of febrile neutropenia in BC patients depending on the systemic treatment regimen (2, 16).

FN risk	Treatment regimen
FN RISK >20%	• TCH-P (docetaxel, carboplatin, trastuzumab, pertuzumab) • TCH (docetaxel, carboplatin, trastuzumab), • TC (docetaxel, cyclophosphamide), • ddAC → T (dose dense doxorubicin + cyclophosphamide - paclitaxel) (only AC part)
FN RISK 10-20%	• AC→T (doxorubicin + cyclophosphamide ->paclitaxel) (only AC q3w part) • PTH (pertuzumab, trastuzumab, docetaxel) • Docetaxel - every 21 days • Sacituzumab govitecan
FN RISK <10%	• CMF (cyclophosphamide, methotrexate, fluorouracil) • Paclitaxel weekly, capecitabine, vinorelbine, gemcitabine, carboplatin • Trastuzumab, pertuzumab • Trastuzumab emtansine • Trastuzumab deruxtecan • Lapatinib, tucatinib • Palbociclib, ribociclib, abemaciclib • Pembrolizumab, atezolizumab • Olaparib, talazoparib • Alpelisib

For some patients the dose-dense treatment regimen may be too intense, taking into account patient's age or comorbidities. It can therefore be stated that such patients are also at higher risk of hematological toxicity and are also candidates for primary FN prophylaxis.

The importance of G-CSF support in dose-dense chemotherapy was also emphasized in the meta-analysis by Yokoe et al. (2025), which confirmed the efficacy and safety of pegfilgrastim prophylaxis in patients with early-stage breast cancer undergoing dose-dense regimens, supporting its routine use in this setting (23).

Another regimen of chemotherapy is combination of docetaxel with cyclophosphamide (TC). In a multicenter, randomized phase II study, the frequency of FN during 6 treatment cycles was significantly lower in the group receiving pegfilgrastim compared to the group without primary prophylaxis (1.2% vs. 68.8%, respectively) (24). It shows that TC regimen is also associated with the highest risk of FN and requires primary prophylaxis with G-CSF is (24). One of the currently recommended treatment regimens for patients with HER2-positive EBC is a combination of docetaxel, carboplatin, and trastuzumab with or without pertuzumab (TCH+/-P) (25).

Numerous studies have assessed the risk of FN during treatment with TCH+/-P regimen. A meta-analysis of 17 studies found that in patients without primary G-CSF prophylaxis, the incidence of FN was 27.6% (95% CI 18.6 to 37.1) compared to 5,0% (95% CI 2.6 to 8.0) in patients receiving G-CSF after each therapy cycle. The TCH+/-P regimen is therefore associated with >20% risk of FN (25–27). According to NCCN and ESMO recommendations, primary prophylaxis is indicated in patients receiving TCH+/-P regimen (2, 6).

Weekly chemotherapy cycles, used in perioperative treatment and in the treatment of advanced BC, do not significantly increase the risk of FN or G3/G4 neutropenia. NCCN guidelines emphasize that in the case of neoadjuvant treatment based on anthracyclines and paclitaxel, further weekly taxane therapy after completion of 4 cycles of dose-dense AC therapy, does not require the use of primary FN prophylaxis (28).

Chemotherapy in metastatic breast cancer

Patients with metastatic breast cancer (MBC) receiving carboplatin or paclitaxel in 3-week cycles have significantly higher FN risk (10-20%) compared to 7-day cycles (20, 29). Patients receiving chemotherapy in 21-day cycles should be managed as the group with intermediate FN risk. Therefore, risk factors should be assessed before each subsequent cycle of therapy.

Indications for the use of metronomic chemotherapy in patients with MBC, which involves prolonged, often oral administration of a low-dose cytostatic agent, were presented in the international ABC recommendations in 2017 (30). Due to the better safety profile, this

therapy is a good choice especially for elderly patients or with multiple comorbidities.

Metronomic chemotherapy involves oral cyclophosphamide (CTX) in combination with methotrexate (MTX) as well as capecitabine and vinorelbine. The multicenter VICTOR-6 study of metronomic therapies in 584 patients with MBC confirmed a very good safety profile of this treatment. Grade 3/4 hematological toxicities (anemia, thrombocytopenia, leukopenia) were observed in only 5.8% of patients, and no episodes of FN were reported (30). Similar results were obtained in a pooled meta-analysis of 22 studies, which assessed 1360 patients with MBC receiving metronomic therapy (31).

In patients with advanced disease, the current treatment duration is significantly longer than previously. Therefore, the risk of FN increases significantly in this patient. Regular assessment of the general health condition in patients treated palliatively may protect them from severe FN complications.

The place of granulocyte colony-stimulating factors in new breast cancer therapies

Triple negative breast cancer

Pembrolizumab

Pembrolizumab is a human IgG4 monoclonal antibody that has been used in the treatment of many cancers. The KEYNOTE-522 and KEYNOTE-355 studies have proven its efficacy in triple-negative breast cancer (TNBC), both in perioperative EBC therapies and in MBC treatment (32, 33).

In the KEYNOTE-522 study, evaluating the efficacy of pembrolizumab in combination with paclitaxel and carboplatin followed by a conventional 3-weekly AC regimen, the incidence of grade ≥3 neutropenia was 34.6% compared with 33.2% in patients receiving chemotherapy alone. FN was reported in 14.6% of patients in the experimental arm and 12.1% in the control group. Similar observations were made in the KEYNOTE-355 study, evaluating the efficacy of pembrolizumab in MBC. The incidence of G3 or higher neutropenia was 41.1% in the pembrolizumab group and 38.1% in the group with chemotherapy alone. The incidence of FN was not reported.

Pembrolizumab does not significantly increase the risk of neutropenia and FN. The initiation of primary or secondary prophylaxis using G-CSFs depends only on the chemotherapy component of combination therapy.

Atezolizumab

Atezolizumab is a humanized IgG1 monoclonal antibody with a modified Fc region directed against PD-L1. Its efficacy in combination with nab-paclitaxel in the treatment of advanced TNBC was demonstrated in the IMpassion130 study (34). The rate of grade 3/4 neutropenia in the experimental arm was 8.2%, the same as in the control group receiving nab-paclitaxel. There were no FN episodes during the study. Due to the low rate of hematological complications, including neutropenia and FN, the use of G-CSF during atezolizumab treatment is not required.

PARP inhibitors (olaparib, talazoparib)

Poly (ADP-ribose) polymerase (PARP) inhibitors have a wide range of indications in patients with HER2-negative BC and confirmed germline *BRCA* mutation (34–36). In clinical trials no significantly higher rates of neutropenia or FN were observed in the experimental arm compared to patients receiving treatment of the investigator's choice. In the OLYMPIA study, a decrease in the white blood cell count (WBC) of grade 3 or higher was observed in only 3% of patients receiving olaparib as adjuvant therapy,. In the OlympiAD study grade 3/4 neutropenia was more frequent in patients receiving chemotherapy of the investigator's choice compared to the study group (35, 36).

In the EMBRACA study, incidence of G3/G4 neutropenia in the experimental arm receiving talazoparib was 20.9%, as compared to significantly higher rate in the control group (35.9%) (62). In none of the above studies G-CSF prophylaxis was required. A small percentage of patients with recurrent neutropenia required a reduction in the PARP inhibitor dose, which resulted in normalization of laboratory results.

Olaparib and talazoparib therapy is not associated with a significant risk of G3/G4 neutropenia and FN. Therefore, neither primary nor secondary prophylaxis with G-CSF is required.

Sacituzumab govitecan

Sacituzumab govitecan (SG) is a conjugate of the monoclonal antibody sacituzumab and the active metabolite of irinotecan (SN-38 molecule) with cytotoxic activity against topoisomerase I.

Phase III ASCENT study confirmed its efficacy in the treatment of advanced TNBC (37). The drug is also approved for the treatment of unresectable or metastatic luminal HER2-negative BC based on the results of the TROPICS-02 study (38). In both studies, G3/G4 neutropenia was the most common treatment-emergent adverse event in the SG arm. In the ASCENT study, it occurred in 51% of patients, compared with 33% in the chemotherapy arm. FN was reported in 6% of patients in the experimental arm and in 2% of patients in the control group. Similar results were obtained in the TROPICS-02 study (G3/G4 neutropenia - 51% vs 33%; FN - 6% vs 3%, respectively). Due to high rates of neutropenia, it was necessary to reduce the dose of SG or to implement secondary FN prophylaxis. G-CSF was used in 49% of patients in the ASCENT study and in 54% of patients in the TROPICS-02 study. Phase II PRIMED study evaluated the effect of G-CSF on reducing the risk of neutropenia and FN associated with SC therapy. The study included 50 patients who received short-acting G-CSF at a dose of 0.5 mg/kg b.w. on days 3–4 and 10–11 during the first two treatment cycles. Grade 3/4 neutropenia occurred only in 8 patients (16%; p=0.0002), and no case of FN was found in the entire group (39).

Based on presented studies, it is recommended to implement G-CSF prophylaxis in case of recurrent neutropenia during SG therapy. However, it should be noted that in order to continue therapy with SG, it is necessary to obtain at least 1,000 G/L of neutrophils on day 8 of the cycle.

HER2 positive breast cancer

Trastuzumab, pertuzumab

The first anti-HER2 drug approved for use in clinical practice was trastuzumab (40, 41). The next step in the development of anti-HER2 therapy was the combination of trastuzumab with another monoclonal antibody, pertuzumab in patients with advanced or MBC. In the CLEOPATRA study, any grade neutropenia, occurred in 53.4% of patients in pertuzumab arm and in 50% of patients in the control group receiving docetaxel in combination with trastuzumab. During further treatment with antibodies alone, neutropenia was observed in 3.3% of patients receiving combined therapy, compared to 5.0% in the control group (42).

FN risk related to trastuzumab and pertuzumab therapy is low, therefore it does not require G-CSF prophylaxis. However, the risk of FN resulting from the chemotherapy used in combination with monoclonal antibodies, should be taken into account.

Trastuzumab emtansine

Trastuzumab emtansine (T-DM1) is a conjugate of the HER2-specific monoclonal antibody trastuzumab and the cytotoxic molecule emtansine. The efficacy and safety of adjuvant therapy were demonstrated in the pivotal study KATHERINE. No significant incidence of hematological toxicities was found and no FN episodes were observed in the study group (43). T In the EMILIA study with patients with MBC, the frequency of G3/G4 neutropenia was only 2% (44). It can be concluded that hematological toxicity (neutropenia) is not a significant complication of T-DM1 therapy. There were no indications for prophylactic use of G-CSF in clinical practice.

Trastuzumab deruxtecan

Trastuzumab deruxtecan (T-DXd) is antibody–drug conjugate (ADC), consisting of HER2-specific monoclonal antibody and topoisomerase I inhibitor deruxtecan., with the efficacy in patients with advanced or metastatic HER2-positive or HER2-low BC confirmed in the DESTINY studies program (45–47).

In T-DXd studies, neutropenia (mainly G1/G2) was a common hematologic adverse event. In the Destiny-Breast03 study, grade 3 or higher neutropenia was observed in 19.1% of patients (46). In in patients with advanced HER2-low BC, the rate of grade 3 or higher neutropenia was 13.7% compared with 40.7% in patients receiving investigator's choice chemotherapy (48). The toxicity during T-DXd treatment is thought to be due to the deruxtecan molecule. Patients with advanced disease are initially at higher risk of developing this complication.

According to ESMO recommendations, T-DXd belongs to the group of drugs with the lowest FN risk (<10%), therefore, the use of G-CSF is not routinely recommended (2). T-DXd treatment can be continued in patients with neutrophil count >1,000 G/L. In patients with recurrent G3/G4 neutropenia, the first step is to consider dose reduction; however, the decision is made on a case-by-case basis. In patients with FN occurring during previous treatment cycles, G-CSF prophylaxis can be considered. However, it should be remembered that in the case of afebrile neutropenia, G-CSF should not be routinely used (48).

Tucatinib

Tucatinib is a potent, selective, and reversible HER2 tyrosine kinase inhibitor, approved in combination with trastuzumab and capecitabine for the treatment of unresectable, locally advanced, or metastatic HER2-positive BC based on phase III HER2CLIMB study. Neither significant hematological toxicities (neutropenia) nor FN episodes were observed in this study (49). Therefore, tucatinib therapy does not require prophylactic G-CSF use in routine clinical practice.

Lapatinib

Lapatinib in combination with capecitabine was registered as a second-line treatment after failure of therapy containing anthracyclines, taxanes, and trastuzumab in patients with advanced, HER2-positive BC based on the pivotal NCT00078572 study. Currently lapatinib is used less often (50, 51). In the pivotal study, the toxicity profile of lapatinib partially overlapped with AEs of capecitabine. The most common AEs included gastrointestinal disorders, rashes, and stomatitis. Neither neutropenia nor FN episodes were observed. Therefore, this therapy does not require the use of G-CSF in clinical practice.

Hormone receptor-positive breast cancer

CDK4/6 inhibitors

The first ciclib registered in clinical practice was palbociclib. The PALOMA pivotal study showed, that it is safe and well-tolerated therapeutic option in advanced luminal HER2-negative BC. The most common AE during palbociclib therapy is hematological toxicity. In the pivotal study, G3/G4 neutropenia was observed in 62% of patients receiving palbociclib in combination with fulvestrant and in 66,5% of patients receiving palbociclib in combination with letrozole. However, the mechanism of CDK4/6 inhibitor toxicity is different from that caused by cytotoxic drugs, and leads to inhibition of granulocyte maturation at the stage of their precursors. The highest risk of neutropenia is associated with the first 15 days of therapy, lasts for 2 treatment cycles, and decreases over time (52, 53).

Ribociclib is highly selective CDK4/6 inhibitor approved for treatment of advanced, luminal BC based on the results of the

MONALEESA studies. Its acceptable safety profile was confirmed in the MONALEESA-2 study. The most common grade 3/4 adverse event was neutropenia (59.3% of patients), with median time to the onset of 16 days. Only 1.5% of patients receiving ribociclib experienced FN (54). Therefore, there is no indication for G-CSF prophylaxis in patients treated with this drug.

Another currently available CDK4/6 inhibitor is abemaciclib, which efficacy and safety were assessed in the MONARCH studies. Abemaciclib is more selective for kinase 4 than for kinase 6, which translates into a slightly different toxicity profile. The incidence of neutropenia is lower than ribociclib and palbociclib. In the pivotal study, the incidence of G3 and G4 neutropenia was 26.8% and 2,9%, respectively: FN was reported in 0.9% of patients (55).

The management algorithm for hematological toxicity, such as neutropenia, is identical for whole CDK4/6 inhibitors class. In the case of recurrent grade 3 or single episode of grade 4 neutropenia, a dose reduction is recommended. There are no indications for prophylactic use of G-CSF (56–58). Importantly, CDK4/6 inhibitors can be safely used when the neutrophil count is ≥1000 G/L.

Alpelisib

Alpelisib is an oral selective inhibitor of the α-isoform of class I phosphatidylinositol 3-kinase (PI3K) (59).

The efficacy of alpelisib in the treatment of advanced luminal HER2-negative BC was assessed in the SOLAR-1 study. Typical toxicities of alpelisib include hyperglycemia, rash, and diarrhea. No significant hematological toxicities were observed during the pivotal study. Therefore, therapy with this drug does not require G-CSF use (60).

Conclusions

G-CSF is currently an integral part of perioperative chemotherapy regimens used in the radical treatment of EBC, possessing high risk of neutropenia and FN. Primary and secondary prophylaxis allows maintaining the appropriate therapy rhythm and dose intensity, which has a direct impact on outcomes. The benefits of using G-CSF has been additionally strengthened by the COVID-19 pandemic. Thanks to these observations, it is easier to make decisions about implementing FN prophylaxis, therefore reducing the risk of significant adverse effects of systemic therapy. Such procedures have translated into a significantly lower risk of FN and related complications. In radical treatment, G-CSF is used primarily in patients receiving dose-dense chemotherapy regimens and TCH+/P regimen.

Hematological toxicities related to MBC treatment have not been a significant clinical problem so far, with the exception of PTH regimen used in first-line treatment of patients with HER2-positive BC, with often prophylactic use of G-CSF. The approval of numerous new targeted therapies, including ADCs, poses new challenges for clinicians. Management algorithms of toxicities associated with the aforementioned therapies also include G-CSF, especially use as a secondary prophylaxis. Better understanding of drugs' mechanisms of action and their characteristic side effects facilitates the implementation and continuation of treatment with modern therapies without unnecessary side effects. Preventing complications protects against premature termination of therapy, which may be a chance for a longer life for BC patients, also with advanced disease.

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AB: Conceptualization, Writing – original draft. ES: Writing – review & editing. ZN: Writing – review & editing. KP: Writing – original draft, Conceptualization.

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