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Postoperative dose-dense sequential chemotherapy with epirubicin, paclitaxel and CMF in patients with high-risk breast cancer: safety analysis of the Hellenic Cooperative Oncology Group randomized phase III trial HE 10/00

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Background: A randomized phase III trial in high-risk breast cancer patients was conducted, to further explore the impact of dose-density in the adjuvant treatment for breast cancer. The safety analysis is presented.
Patients and methods: From October 2000 until June 2005, 1121 node-positive patients were randomized to sequential dose-dense epirubicin 110 mg/m^2 and paclitaxel (Taxol®, Bristol Myers-Squibb, Princeton, New Jersey, USA) 250 mg/m^2 (group A), or concurrent epirubicin 83 mg/m^2 and paclitaxel 187 mg/m^2 (group B), both followed by three cycles of 'intensified' combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF). Granulocyte colony-stimulating factor was given prophylactically with the dose-dense treatments.
Results: Median dose intensity of epirubicin and paclitaxel was double in group A, as designed, with significantly less cycles administered at full dose ($P < 0.001$). Median cumulative dose of all drugs and total treatment duration, however, were identical between groups. Severe taxane-related toxic effects were more frequent in group A, while severe thrombocytopenia was low and present only in group A. There were no differences in the rates of other hematological toxic effects, including febrile neutropenia. The rates of secondary malignancies were low.
Conclusion: Both regimens as used in the present study are well tolerated and safe. The rates of severe taxane-related toxic effects and thrombocytopenia, although low overall, are significantly increased with the dose-dense sequential regimen.
Key words: breast cancer, chemotherapy, epirubicin, paclitaxel, randomized phase III trial, taxanes

introduction

Breast cancer is the most common malignancy in European women today [1], although the yearly incidence in the United States of America is declining [2]. The modern era of clinical research on the treatment for breast cancer is characterized by two major advantages: the conceptualization of new principles, such as dose-density and sequential chemotherapy [3], and the development of new active drugs, such as the taxanes i.e. paclitaxel or docetaxel [4].

The first evidence of the beneficial effect of sequential chemotherapy in high-risk breast cancer came from the studies of the Milan group [5]. More recently, the Intergroup trial 0148 [6] demonstrated that four cycles of paclitaxel every 3 weeks following four cycles of doxorubicin and

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cyclophosphamide (AC) were superior to four cycles of AC alone on the 5-year disease-free survival (DFS) and overall survival (OS). These results, however, were challenged by the fact that the duration of treatment and the number of drugs were not identical in both groups.

The role of dose-density [the increase of dose intensity (DI) by reducing the interval between cycles] was initially evaluated with the introduction of granulocyte colony-stimulating factors (G-CSFs) in the early 90s. Pioneered by the Memorial Sloan Kettering Cancer Center [7] and followed by other groups including ours [8], the feasibility of adjuvant dose-dense sequential regimens was clearly demonstrated in high-risk breast cancer patients, leading to the pivotal C9741 trial, which showed the superiority of dose-dense adjuvant treatment over conventional chemotherapy [9]. The Hellenic Cooperative Oncology Group (HeCOG) recently published the results of a randomized phase III trial [10], exploring the benefit from the addition of paclitaxel (Taxol®, Bristol Myers-Squibb, Princeton, NJ) to a dose-dense sequential regimen of epirubicin followed by 'intensified' combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF). As in the Intergroup trial 0148 [6], our results were confounded by the different number of drugs and duration of treatment in the two study arms.

In order to further explore the impact of DI in the adjuvant setting of breast cancer, we designed a randomized phase III trial in patients with node-positive breast cancer. The sequential dose-dense administration of epirubicin followed by paclitaxel was compared with the concurrent standard three-weekly administration of the two drugs, in both cases followed by intensified CMF. In this report we present the results of the safety analysis.

patients and methods

eligibility criteria

Patients with histologically confirmed epithelial breast cancer; pathological stage $T_{1-4}N_{1-2}M_0$; Eastern Cooperative Oncology Group performance status of zero to one; normal cardiac function and adequate bone marrow, hepatic and renal function were eligible. Patients with a history of malignancy other than completely excised *in situ* carcinoma of the cervix, basal carcinoma of the skin, inflammatory breast cancer, serious cardiac disease, other serious medical illness or inability to comply with the treatment plan and follow-up visits were not eligible.

The clinical protocol was approved by the HeCOG Protocol Review Committee, by appropriate Institutional Review Boards at participating Institutions and by the National Organization for Medicines, Division of Pharmaceutical Studies and Research. Written informed consent was obtained from all patients.

Pretreatment evaluation included medical history, physical examination, chest X-rays, liver ultrasound (or computed tomography scan in case of more than nine positive nodes), bone scans, ejection fraction (EF) measured by nuclear-gated heart scan or by echocardiogram, complete blood count (CBC) and biochemistry. CBC and biochemistry were repeated before each cycle and EF after the completion of all cycles.

treatment

Stratified randomization balanced by center was carried out at the HeCOG Data Office in Athens, using the following stratification factors: menopausal status (premenopausal versus postmenopausal), hormonal receptor status (positive versus negative) and number of positive nodes (one to three versus four or more). Postmenopausal were considered patients without menses for the last 2 years or patients >50 years of age who underwent a hysterectomy for reasons other than the existence of malignancy.

The chemotherapy regimens are depicted in Figure 1. Ondansetron + dexamethasone were used as antiemetics. Tamoxifen, 20 mg/day orally, was prescribed for 5 years in all hormonal receptor-positive patients. All premenopausal patients underwent ovarian suppression for 2 years. Following the publication of the results of the International Exemestane Study [11], the protocol was modified and postmenopausal patients, after 2–3 years of tamoxifen, were switched to two to three additional years of exemestane 25 mg/day orally. Radiation therapy (RT) was mandatory for all patients with breast-conserving surgery or for those with four or more positive lymph nodes and/or tumor size ≥5 cm (irrespective of the type of initial operation). The RT technique was previously described [10]. Treatment with tamoxifen, ovarian suppression and RT followed chemotherapy completion.

dose modifications

CBC and complete biochemistry were carried out before each cycle. CBC was repeated between cycles only in case of fever >38°C, severe stomatitis or diarrhea. Dose modifications were carried out as previously described [10]. Toxicity criteria were those adopted by the World Health Organization.

follow-up

Patients were followed with a physical examination, CBC, biochemistry and CA 15–3 determination, every 3 months for the first 2 years and every 6 months thereafter. Chest X-rays, ultrasonography of the abdomen and bone scans were repeated every 6 months for the first 3 years and annually thereafter. Mammography was repeated annually. Bone scans were not routinely carried out after the third year, except when clinically indicated.

statistical methods

For a two-sided test at the 5% level of significance and power of 80%, the number of patients required to detect a difference between the two treatment arms within 5% (±2.5%) to the baseline rate of 80% in DFS at the 3-year time point was 1040 patients. Taking into consideration a 5% withdrawal, 1100 patients (550 per group) needed to enter the study. The study accrual rate was estimated at 230 per year and the maximum study duration was estimated to be 8 years, for observing a total of 324 relapses. An interim analysis based on the O'Brien Fleming boundary values was to be carried out when 50% of the end points had been reached along with the safety analysis.

DFS was defined as the interval from study entry to first locoregional recurrence, first distant metastasis, contralateral breast cancer, secondary neoplasm, death from the disease or death from any cause nonrelated to breast cancer, whichever occurred first. OS was measured from study entry until death from any cause. Surviving patients were censored at the date of last contact. Survival status was updated in September 2006 and the safety analysis reported here was carried out at the scheduled interim analysis. The study was not ended prematurely at the interim analysis and follow-up is ongoing to study completion. Differences between groups were evaluated by Fisher's exact test for categorical variables and Mann–Whitney *U* test for continuous variables (two-sided tests).

Patient information was collected on standard HeCOG study forms by authorized data managers and entered in the HeCOG database. The trial was monitored by certified HeCOG personnel.

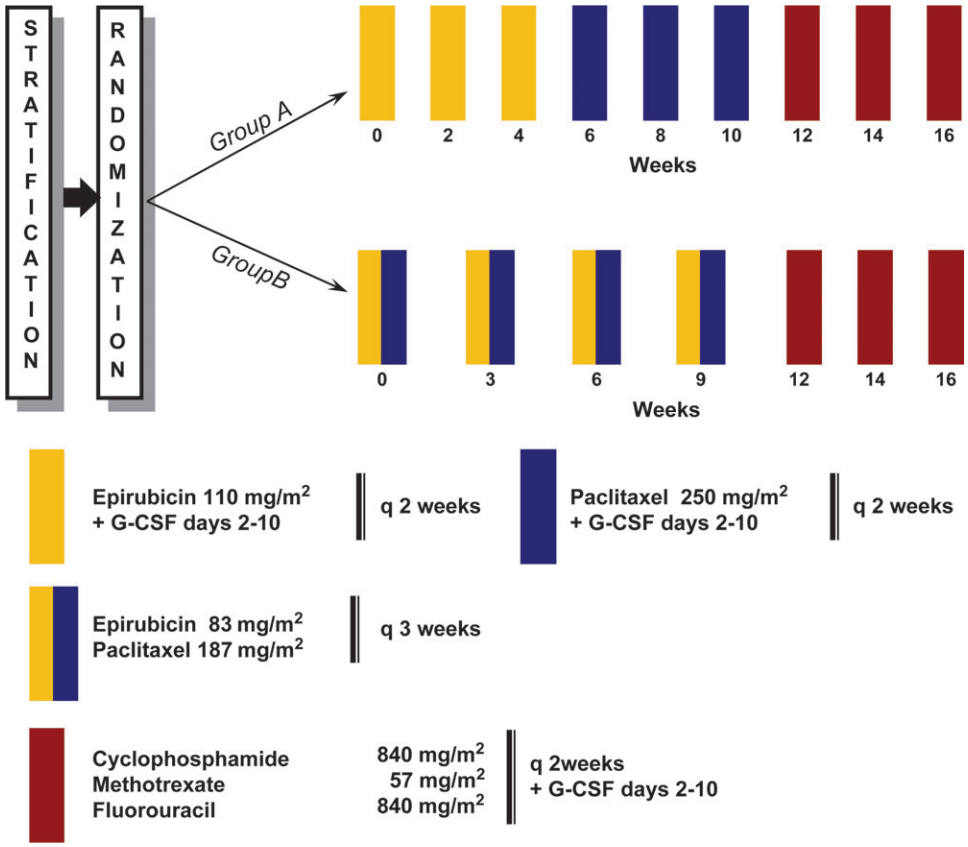

Figure 1. Treatment schema.

results

From October 2000 until June 2005, 1121 patients were randomized. Thirty-five patients were found noneligible. Reasons for noneligibility were the presence of metastatic disease at the time of randomization (12 patients), history of other cancer [6], bilateral breast cancer [7], inflammatory breast cancer [4], left ventricular EF <50% [2], N_0 disease [2], administration of RT before chemotherapy [1] and simple mastectomy without axillary clearance in one patient.

The progress of patients through the various stages of the trial is shown in the flow diagram, Figure 2, according to the Consolidated Standards of Reporting Trials [12]. The safety analysis presented here was carried out on 1063 patients, excluding 14 patients who never started treatment and 9 with incomplete treatment and toxicity data in their medical files. Eleven patients received the opposite treatment than the one allocated to and were analyzed for safety and toxicity according to the actual treatment given. All analyses were carried out according to the intention-to-treat principle.

The two treatment groups were well balanced with respect to patient and tumor characteristics, as shown in Table 1. Most of the patients (73%) had hormone-responsive disease. Selected treatment characteristics are depicted in Table 2. Significantly more cycles were administered at full dose in group B (group A: 65% versus group B: 77%, $P < 0.001$), while the percentage of cycles given with a delay was significantly higher in group A (group A: 21% versus group B: 17%, $P < 0.001$).

Median DI of epirubicin and paclitaxel was double in group A, as designed. Median duration of chemotherapy was 18 weeks in both groups. Moreover, median cumulative doses of all drugs were almost identical in both groups (epirubicin, 330 mg; paclitaxel, 746 mg; cyclophosphamide, 2517 mg; methotrexate, 170 mg and fluorouracil, 2517 mg).

Severe (grade 3 or 4) hematological and non-hematological side-effects are shown in Table 3. Severe thrombocytopenia was recorded only in patients of group A (group A: 1.1% versus group B: 0%, $P = 0.03$). Severe sensory neuropathy (group A: 9.5% versus group B: 2.1%, $P < 0.001$) and hypersensitivity reactions (group A: 5.2% versus group B: 1.4%, $P < 0.001$) were more frequently recorded in group A, probably due to the higher dose of paclitaxel.

Significantly more patients in group A reported severe arthralgias/myalgias (group A: 3% versus group B: 0.8%, $P = 0.01$). Overall, 56 patients (5%) had developed febrile neutropenia [group A: 25 (4.6%), group B: 31 (5.9%)]. One patient in group A died 15 days after treatment completion from gastrointestinal bleeding.

In total, 78 patients (7%) (41 in group A versus 37 in group B) were hospitalized for a variety of reasons. Data on hospitalizations, antibiotic administration and platelet and red blood cells (RBCs) transfusions were reported for all patients, while information on supportive care was collected from selected centers on a total of 941 patients (group A: 479, group B: 462) with available safety data.

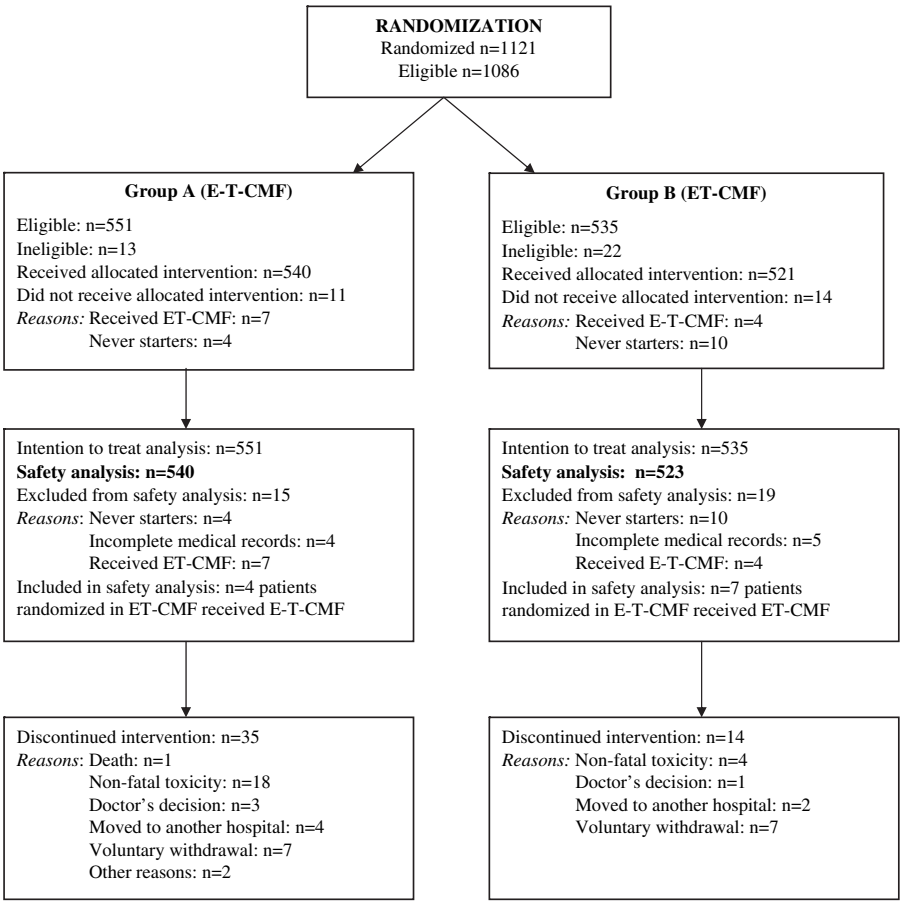

Figure 2. Progress through the various stages of the trial.

Antibiotics were administered to 175 patients (16.5%) (87 in group A versus 88 in group B). Furthermore, 25 patients were transfused with RBC [(17 (3%) in group A versus 8 (1.5%) in group B], while 2 patients in group A received platelet transfusions. A total of 272 patients received erythropoietin for treatment or prophylaxis of chemotherapy-induced anemia, with no significant differences between the 2 groups [150 (31%) in group A versus 122 (26%) in group B].

Forty-nine patients discontinued chemotherapy with significantly more patients in group A [35 (6.5%) versus 14 (3%) in group B ($P = 0.003$)]. Among those who discontinued, permanent treatment interruption due to toxicity was reported in 18 patients (51%) in group A and in 4 patients (29%) in group B ($P = 0.21$). One patient in group A died from lobular pneumonia, after the first cycle of paclitaxel. According to her physician, her death could not be attributed to the treatment.

In group A, three patients discontinued treatment during epirubicin administration, one after two cycles due to severe febrile neutropenia (grade 4) and the other two after the first epirubicin infusion. One of them had a history of medically controlled angina with normal pretreatment EF. A diagnosis of 95% stenosis of the left coronary artery was made and the patient fully recuperated after angioplastic surgery. The second patient was admitted to the hospital with excessive dyspnea and a diagnosis of acute pulmonary embolism was established. No predisposing factors were identified. The patient was successfully treated with i.v. heparin.

Eighteen patients discontinued treatment during administration of paclitaxel, 17 of them due to neurotoxicity grade 3 or grade 4 [10 after the first cycle (one with grand mal seizures) and 7 after the second] and 1 due to severe neutropenia (grade 4). In 10 of the 18 patients, treatment was interrupted permanently, while in the remaining 8 patients treatment was continued with CMF.

Four patients discontinued treatment during CMF. One of them demonstrated a grade 3 allergic reaction with facial erythema, cough, dyspnea, bronchospasm and hypotension during the first methotrexate infusion. She discontinued treatment and was given antihistamines and hydrocortisone. The other three patients discontinued after the second CMF cycle, one due to neurotoxicity grade 3, one due to neutropenia grade 4 and mucositis grade 3 and one following drug extravasation.

In group B, two patients discontinued treatment permanently due to neurotoxicity grade 3 or grade 4, one of them after the first Epirubicin-Taxol (ET) cycle and one after the fourth cycle. Additionally, one patient developed a grade 4 allergic reaction after the first ET cycle and one grade 3 transaminasemia after the second CMF cycle. They both decided to stop further treatment. Moreover, one patient

Table 1. Selected patient and tumor characteristics

	Group A (E–T–CMF)		Group B (ET–CMF)	
N	540		523	
Age (years)				
Median	52		54	
Range	24–79		22–77	
Number of nodes removed				
Median	17		16	
Range	1–54		1–46	
Number of positive nodes				
Median	4		3	
Range	1–40		1–40	
	N	%	*N*	%
1–3 nodes	260	48	258	49
≥4 nodes	280	52	265	51
Menopausal status				
Premenopausal	254	47	235	45
Postmenopausal	286	53	288	55
Type of operation				
Modified radical mastectomy	350	65	339	65
Breast-conserving surgery	190	35	184	35
Interval from operation				
<2 weeks	38	7	42	8
2–4 weeks	238	44	235	45
>4 weeks	262	48.5	246	47
Not specified	2	0.4	–	–
ER status				
Negative	168	31	162	31
Positive	370	68.5	361	69
Not specified	2	0.4	–	–
PR status				
Negative	218	40	194	37
Positive	319	59	328	63
Not specified	3	1	1	0.2
Hormonal receptor status				
Negative	143	26.5	138	26
Positive	395	73	385	74
Not specified	2	0.4	–	–
HER-2 overexpression				
No	346	64	330	63
Yes	175	32	176	34
Not specified	19	3.5	17	3
Tumor size (cm)				
Median	2.7		2.6	
Range	0.2–14.8		0.2–14.0	
	N	%	*N*	%
≤1.0	27	5	22	4
1.1–2.0	143	26.5	150	29
2.1–3.0	170	31.5	163	31
3.1–5.0	141	26	132	25
>5.0	57	11	55	10.5
Not specified	2	0.4	1	0.2
Nuclear grade				
I	32	6	32	6
II	245	45	242	46
III	261	48	248	47
IV	1	0.2	–	–
Not specified	1	0.2	1	0.2

E, epirubicin; T, paclitaxel (Taxol); CMF, combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil; ER, estrogen receptor; PR, progesterone receptor.

Table 2. Selected treatment characteristics

	Group A (E–T–CMF)	Group B (ET–CMF)
N	540	523
Number of cycles delivered	4674	3616
Median	9	7
Range	1–10	1–9
Percentage of cycles given at full dose[a]	65	77
Percentage of cycles given with dose reduction	35	23
Percentage of cycles given with a delay	21	17
Median interval between cycles (days)	14	21
Median delivered DI[b]		
E	54 (55)	27 (27.5)
T	122 (125)	61 (62)
C	412 (420)	410 (420)
M	28 (28.5)	28 (28.5)
F	412 (420)	410 (420)
Median RDI		
E	0.98	0.98
T	0.98	0.98
C	0.98	0.98
M	0.97	0.97
F	0.98	0.98

[a]≥90% of the dose defined in the protocol.
[b]Numbers in parentheses indicate initially planned DIs.
E, epirubicin; T, paclitaxel (Taxol); CMF, combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil; DI, dose intensity mg/m^2/week); RDI, relative dose density.

after the first ET cycle and five more after the third discontinued treatment because of moderate but persistent symptoms, such as neurotoxicity, arthralgias/myalgias, fatigue and allergic reaction. The above six patients continued chemotherapy with CMF.

After a median follow-up of 40 months, 190 patients (18%) had documented disease progression and 88 patients (8%) had died. In most cases (79 of 88 deaths), cause of death was the disease. Two patients died during the chemotherapy period, as previously stated, one from gastrointestinal bleeding and one due to acute respiratory infection after the first cycle of paclitaxel. One patient died from a second malignancy (endometrial cancer), five from other reasons (three due to a stroke, one due to cardiac disease and one from massive pulmonary embolism), while for one patient the cause of death was unknown.

Overall, nine patients developed a second malignancy, six in group A and three in group B. One case of acute myelogenous leukemia (AML) was reported in a patient of group A, one case of colorectal cancer, one of lung cancer, one of endometrial cancer and one of ovarian cancer. Furthermore, four patients developed contralateral breast cancer, two in each treatment group.

Table 3. Incidence of severe toxic effects

	Group A (E–T–CMF)				Group B (ET–CMF)			
N	540				523			
	Grade 3		Grade 4		Grade 3		Grade 4	
	N	%	*N*	%	*N*	%	*N*	%
Anemia	9	1.7	–	–	2	0.4	1	0.2
Leukopenia	50	9.3	11	2.0	48	9.2	8	1.5
Neutropenia	70	13.0	52	9.6	53	10.2	60	11.5
Thrombocytopenia*	4	0.7	2	0.4	–	–	–	–
Nausea/vomiting	14	2.6	1	0.2	16	3.1	–	–
Fatigue	2	0.4	–	–	6	1.1	–	–
Infection	2	0.4	24	4.4	1	0.2	31	5.9
Cardiotoxicity	1	0.2	–	–	1	0.2	–	–
CNS	1	0.2	–	–	–	–	–	–
Pulmonary	–	–	1	0.2	–	–	–	–
Peripheral neuropathy**	49	9.1	2	0.4	10	1.9	1	0.2
Hepatotoxicity	7	1.3	–	–	4	0.8	–	–
HSRs***	25	4.6	3	0.6	4	0.8	3	0.6
Mucositis	12	2.2	1	0.2	12	2.3	–	–
Arthralgias/myalgias****	16	3.0	–	–	4	0.8	–	–
Pain	–	–	–	–	1	0.2	–	–

Alopecia was universal.

*$P = 0.03$; **$P < 0.001$; ***$P < 0.001$; ****$P = 0.01$.

E, epirubicin; T, paclitaxel (Taxol); CMF, combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil; CNS, central nervous system; HSR, hypersensitivity reactions.

discussion

Dose intensification has been shown to correlate with patient outcome in adjuvant chemotherapy for breast cancer [13] and dose-dense anthracycline–taxane-containing regimens are among the current adjuvant treatments of choice in high-risk node-positive breast cancer. The optimal combinations and sequence of administration, however, are still under investigation [4]. The present study was designed on the basis of previous experience from our group [10], in order to compare the administration of a sequential dose-dense schedule with the concurrent combination schedule using the same agents, at the same cumulative doses and the same total duration of adjuvant treatment. Most previous dose-dense trials demonstrated the feasibility of the approach, but were limited by their design, either lacking power or utilizing different numbers of agents and duration in the treatment arms [14, 15].

Following the pivotal Cancer and Acute Leukemia Group B (CALGB) 9741 study, several issues remained to be investigated, including acute and late toxicity, the effect of G-CSF support, the cost over therapeutic benefit and the choice of taxane and anthracycline. A number of these issues are addressed in ongoing trials including ours.

The analysis presented here is addressing some of the open safety issues. The median chemotherapy duration in our study was 18 weeks, the same in both arms, and the median cumulative dose of all drugs was virtually identical, while, by design, the median DIs of epirubicin and paclitaxel were double in the dose-dense arm. As expected and in accordance with other studies [16], more patients experienced treatment delays or dose reductions with the dose-dense regimen, with significantly more cycles being delivered at full dose in the other arm.

The most common severe side-effect in our study, balanced between groups, was neutropenia, while the rate of febrile neutropenia (5%) was similar to the 2%–3% reported in the CALGB 9741 study [9].

Preliminary results of recent trials, such as the Breast Cancer International Research Group (BCIRG) 005 and the Breast International Group 2-98, demonstrated that doxorubicin followed by docetaxel followed by CMF results in DFS benefit as well as lower rates of febrile neutropenia compared with a concurrent anthracycline–taxane regimen followed by CMF [17, 18]. The use of pegfilgrastim, although not established, has being proposed with dose-dense regimens [19, 20]. In a recent report of 5510 breast cancer patients receiving adjuvant chemotherapy, the use of G-CSF was associated with a doubling in the risk of AML or myelodysplastic syndrome, raising concerns about the risks of G-CSF use [21]. In our study, after a 40-month median follow-up, there was one case of AML in the dose-dense arm, 2 years after chemotherapy completion.

Severe thrombocytopenia was low and only reported in arm A, while severe anemia was low in both arms (1.7% and 0.6%). This compares favorably with the CALGB 9741 trial, where the transfusion rate in the dose-dense arm was high (13%), while no information was available on erythropoietic support [9].

In our study, a total of 78 patients (7%) were hospitalized for a variety of reasons, with no significant differences

between groups. Similarly, except for the use of G-CSF, there were no significant differences between treatment groups on any other supportive care.

Severe cardiotoxicity was reported only in two of our patients (0.2% in each arm), identical to the rate of the Italian study by Venturini et al. [22]. In the CALGB 9741 and the National Surgical Adjuvant Breast and Bowel Project B28 trials, severe cardiotoxicity was slightly higher (1%–1.6%), possibly due to the use of doxorubicin. It is well established that cardiotoxicity increases with increasing anthracycline doses and when doxorubicin is combined with paclitaxel. Paclitaxel strongly stimulates the conversion of doxorubicin to toxic metabolites in cardiac tissue, but not that of epirubicin, indicating that in taxane combinations, epirubicin may be a safer choice [23].

In our study, taxane-specific severe toxic effects were significantly more common in the dose-dense group, possibly due to the higher dose of paclitaxel in this arm. In fact, during paclitaxel administration in group A, a total of 16 patients discontinued treatment due to neurotoxicity, compared with only three in group B. The above rates are only slightly higher than those seen in other trials. In the CALGB 9741 trial, postchemotherapy neurotoxicity was rare overall, but was more frequent in the concurrent than in the sequential regimen (4% versus 2%, $P = 0.005$). The dose of paclitaxel in our study was higher in both arms than in other dose-dense studies (250 mg/m^2 in the sequential arm and 187 mg/m^2 in the concurrent arm, compared with a conventional 175 mg/m^2 in the CALGB 9741 study), showing that the approach of dose-intense and dose-dense paclitaxel administration is both feasible and safe.

Two deaths occurred in our study, both in group A, during or immediately after the chemotherapy treatment period, while the incidence of second primary malignancies and AML was in line with previous reports [24, 25].

In conclusion, this safety analysis demonstrated that both regimens as used in the present study are feasible and safe. These toxicity and safety results remain to be revisited in the context of evaluating the efficacy of the regimens, as expressed by DFS and OS. Important issues, such as the optimal use of G-CSF and the optimal dose and sequence of the chemotherapeutic drugs, should be further evaluated in future randomized trials.

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