

Gemcitabine, Epirubicin, and Paclitaxel Versus Fluorouracil, Epirubicin, and Cyclophosphamide As First-Line Chemotherapy in Metastatic Breast Cancer: A Central European Cooperative Oncology Group International, Multicenter, Prospective, Randomized Phase III Trial

Christoph Zielinski, Semir Beslija, Zrinka Mrcic-Krmpotic, Marzena Welnicka-Jaskiewicz, Christoph Wiltchke, Zsuzsanna Kahan, Mislav Grgic, Valentina Tzekova, Moshe Inbar, Jozika Cervek, Ivan Chernozemsky, Janos Szanto, Stanislav Spanik, Maria Wagnerova, Nicolae Ghilezan, Janusz Pawlega, Damir Vrbanc, Dmitry Khamtsov, Victoria Soldatenkova, and Thomas Brodowicz

From the University Hospital Vienna, Vienna, Austria; Institute of Oncology, Sarajevo, Bosnia; University Hospital, Zagreb, Croatia; Medical University, Gdansk; Jagiellonian University, Krakow, Poland; Onkoterápiás Klinika, Szeged; Debrecen Medical University, Debrecen, Hungary; University Hospital "Queen Joanna"; National Oncological Center, Sofia, Bulgaria; Sourasky Medical Center, Tel Aviv, Israel; Institute of Oncology, Ljubljana, Slovenia; Nemocnica Saetes Alzbety, Bratislava; Fakultna Nemocnica Luisa Pasteura, Kosice, Slovakia; Institute of Oncology, Cluj, Romania; and InnoPharm, Smolensk, Russia.

Submitted December 16, 2003; accepted November 30, 2004.

Supported by grants from Eli Lilly and Company, Bristol-Myers Squibb, and Pharmacia Upjohn.

Presented in part at the 39th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 3, 2003.

Statistical analysis was performed by D.K. and V.S. from InnoPharm, Smolensk, Russia.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Christoph C. Zielinski, MD, Department of Medicine I, University Hospital, 18-20 Waehringer Guertel, A-1090 Vienna, Austria; e-mail: christoph.zielinski@meduniwien.ac.at.

© 2005 by American Society of Clinical Oncology

0732-183X/05/2307-1401/\$20.00

DOI: 10.1200/JCO.2005.12.106

A B S T R A C T

Background

The objectives of this phase III trial were to compare the time to progressive disease (TtPD), overall response rate (ORR), overall survival, and toxicity of gemcitabine, epirubicin, and paclitaxel (GET) versus fluorouracil (FU), epirubicin, and cyclophosphamide (FEC) as first-line therapy in patients with metastatic breast cancer (MBC).

Patients and Methods

Female patients aged 18 to 75 years with stage IV and measurable MBC were enrolled and randomly assigned to either gemcitabine (1,000 mg/m², days 1 and 4), epirubicin (90 mg/m², day 1), and paclitaxel (175 mg/m², day 1) or FU (500 mg/m², day 1), epirubicin (90 mg/m², day 1), and cyclophosphamide (500 mg/m², day 1). Both regimens were administered every 21 days for a maximum of eight cycles.

Results

Between October 1999 and November 2002, 259 patients (GET, n = 124; FEC, n = 135) were enrolled. Baseline characteristics were well balanced across treatment arms. After a median of 20.4 months of follow-up, median TtPD was 9.1 months and 9.0 months in the GET and FEC arms, respectively (*P* = .557). The ORR was 62.3% in the GET arm (n = 114) and 51.2% in the FEC arm (n = 129; *P* = .093). Grade 3 and 4 toxicities, including neutropenia, thrombocytopenia, anemia, stomatitis, neurosensory toxicity, and allergy, occurred significantly more often in the GET arm.

Conclusion

No significant differences in terms of TtPD and ORR were observed between the two treatment arms. Treatment-related toxicity was higher in the GET arm.

J Clin Oncol 23:1401-1408. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Breast cancer is the most common malignancy and the leading cause of European female cancer mortality.¹ Although the breast cancer incidence has declined in many areas of the

world, this disease still remains a significant health risk to women.² Despite availability of hormonal, chemotherapeutic, and biologic agents, metastatic breast cancer (MBC) remains essentially incurable, with less than 10% of patients being disease free beyond 5 years.^{3,4}

An important step in the treatment of MBC was the introduction of anthracycline-based chemotherapeutic combination regimens that resulted in increased response rates (RRs) and time to progressive disease (TtPD) compared with nonanthracycline-containing combinations or monotherapy.⁵ Doxorubicin-related cardiotoxicity was reduced by the introduction of epirubicin without compromising RR, response duration, TtPD, and overall survival (OS).^{6,7} Consequently, doxorubicin or epirubicin have been considered the backbone of cytotoxic treatment regimens for MBC patients and are often combined with other cytotoxic agents, mainly fluorouracil (FU) and cyclophosphamide, to form the FU, doxorubicin, and cyclophosphamide and the FU, epirubicin, and cyclophosphamide (FEC) regimens. These regimens have produced RRs of approximately 50% and were, therefore, largely accepted as standard treatment for MBC.⁵⁻⁷

The introduction of paclitaxel and docetaxel in the 1990s added another effective treatment option for MBC. Anthracycline and paclitaxel combination regimens have produced RRs of more than 80% in phase II trials.^{8,9} However, impressive RRs observed in single-institution phase II MBC trials have rarely been confirmed in subsequent multi-institution phase II or phase III trials. Within this context, improved OS was observed in one phase III trial,¹⁰ whereas the majority of phase III studies did not show an improvement in OS.¹¹⁻¹⁴ Moreover, the results were complicated by a high incidence of congestive heart failure (> 20%),^{8,10} which was probably a result of paclitaxel-induced decreased clearance of anthracyclines and their metabolites,¹⁵ necessitating modifications of dose¹³ or treatment schedule.¹⁰

Given these considerations, it is important to aim for treatment schedules that increase RRs and prolong TtPD and OS, without simultaneously increasing toxicity and, in particular, cardiotoxicity. One potential candidate for such a regimen is the combination of gemcitabine, epirubicin, and paclitaxel (GET), which has shown an RR of 92% in a phase II study of patients with MBC.¹⁶ The GET regimen was developed on the basis of previous observations of considerable activity and limited toxicity of gemcitabine as first-, second-, and even third-line treatment in phase II studies of MBC.¹⁷ Thus, the addition of gemcitabine to epirubicin and paclitaxel was speculated to increase activity of the combination without additional toxicity.¹⁵ Within this context, the Central European Cooperative Oncology Group conducted a multicenter phase III study in which the efficacy and toxicity of first-line GET and FEC were compared in anthracycline-naïve MBC patients.

PATIENTS AND METHODS

Eligibility Criteria

Patients aged 18 to 75 years with histologically and/or cytologically confirmed stage IV MBC were eligible. Patient selection was irrespective of hormone receptor status and menopausal status. Disease must have been bidimensionally or unidimensionally

measurable either by physical examination or radiologic evaluation. Prior chemotherapy was limited to one adjuvant nonanthracycline-containing regimen. Patients with prior adjuvant chemotherapy must have relapsed more than 6 months after treatment. Prior chemotherapy for metastatic disease was not allowed. Patients with asymptomatic brain metastasis and/or nonmeasurable bone metastasis were eligible only if other measurable or assessable disease existed. Previous surgery, hormonal therapy, localized radiotherapy, or immunotherapy was allowed, but immunotherapy and radiotherapy must have been completed before study entry (4 weeks and 2 weeks, respectively). Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and a 12-week minimum life expectancy. Additional eligibility criteria included adequate hematologic (absolute neutrophil count [ANC] $\geq 1.5 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$), renal and hepatic (creatinine and total bilirubin $\leq 1.25 \times$ upper limit of normal), and cardiac function (left ventricular ejection fraction $\geq 50\%$ by echocardiogram). Finally, patients were required to be available for treatment and follow-up.

Patients were excluded if they had a prior or current history of neoplasm other than breast cancer (except for nonmelanoma skin cancer or curatively treated carcinoma-in-situ of the uterine cervix). Patients were also excluded for any of the following reasons: prior taxane therapy, atrial or ventricular arrhythmias, congestive heart failure, myocardial infarction, allergic reactions to drugs containing polyethoxyethylated castor oil, pre-existing motor or sensory neurotoxicity more than grade 1 (WHO criteria), active infection, inability to receive protocol treatment because of serious underlying medical conditions, or pregnant or breastfeeding.

Each patient provided written informed consent according to local investigational review board requirements before study enrollment. The study was conducted according to the most recent version of the Declaration of Helsinki and any applicable regulations and guidelines.

Study Design and Treatment

Within this multicenter phase III study, patients were randomly assigned to GET or FEC via a centralized randomization system based on a minimizing algorithm¹⁸ and stratified by prior adjuvant chemotherapy (none *v* adjuvant) and center. Study design, including doses, schedules, and maximum number of cycles for each arm, is illustrated in Figure 1. Patients were discontinued from treatment in case of unacceptable toxicity, intercurrent illness, or other reasons that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree, or by patient request.

Patients on the GET arm were premedicated with dexamethasone 20 mg orally (or equivalent) 12 and 6 hours before paclitaxel, diphenhydramine 50 mg intravenously 30 minutes before paclitaxel, and cimetidine-ranitidine 300 mg and 50 mg, respectively, intravenously 30 minutes before paclitaxel. Antiemetics were administered according to local practice. Colony-stimulating factors were administered to patients as appropriate. No other anticancer drugs were allowed during the study, including hormonal agents and/or immunotherapy. Palliative radiotherapy was permitted as long as the indicator lesion was outside the irradiated field.

Dose Adjustments

Dose reductions were performed in the event of cytopenia (ANC $< 0.5 \times 10^9/L$ and/or platelet count $< 50 \times 10^9/L$ lasting ≥ 7 days and/or documented infection and/or severe bleeding), febrile neutropenia (fever $\geq 38^\circ C$ and ANC $< 0.5 \times 10^9/L$ requiring

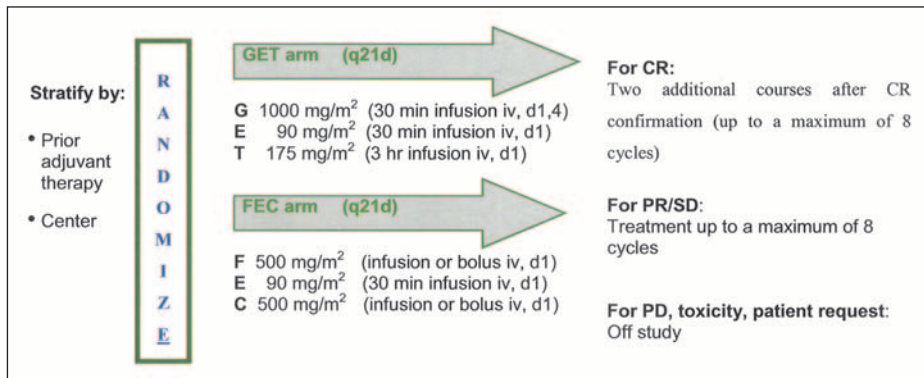


Fig 1. Study design. GET, gemcitabine, epirubicin, and paclitaxel; CR, complete response; iv, intravenously; FEC, fluorouracil, epirubicin, and cyclophosphamide; PR/SD, partial response/stable disease; PD, progressive disease.

anti-infective treatment), or WHO grade 3 mucositis. In the event of WHO grade 3 neurologic toxicity, only the paclitaxel dose was reduced.

For both arms, doses were adjusted for hematologic and nonhematologic toxicities according to three predefined dose levels (0, -1, and -2). Patients' doses were reduced from dose level 0 (starting doses) to dose level -1 (GET: gemcitabine 800 mg/m², epirubicin 75 mg/m², paclitaxel 150 mg/m²; FEC: FU 500 mg/m², epirubicin 75 mg/m², cyclophosphamide 400 mg/m²) if toxicity occurred and then further reduced to dose level -2 (GET: gemcitabine 800 mg/m², epirubicin 60 mg/m², paclitaxel 150 mg/m²; FEC: FU 400 mg/m², epirubicin 60 mg/m², cyclophosphamide 400 mg/m²) if toxicity necessitated any additional dose reductions. The next cycle was not started unless ANC was $\geq 1.5 \times 10^9/L$, and the platelet count was $\geq 100 \times 10^9/L$. If hematologic recovery was achieved before day 42, the patient received full doses or was otherwise discontinued from treatment.

Baseline and Treatment Assessments

At least 2 weeks before randomization, medical history, physical examination, ECOG performance status assessment, tumor measurement, CBC, blood chemistries, ECG, echocardiogram, and toxicity assessments using WHO criteria were performed. The same method used to assess disease status at baseline was used throughout the study.

All patients had a CBC drawn weekly. Physical examination, ECOG performance status assessment, and blood chemistries were performed on day 1 of every cycle. Tumor imaging and response assessment were carried out every other cycle. In addition, ECG (as necessary), echocardiogram (before cycles 5 and 7 and at study completion), and toxicity (after each cycle) were assessed. Upon completion of treatment, follow-up was performed every 2 months.

Tumor measurement was carried out according to standard WHO criteria. Time to response was defined as the interval between the dates of randomization and first documented complete response (CR) or partial response (PR). Response duration was defined as interval between the dates of first documented CR or PR and first documented sign of disease progression. Only confirmed CRs or PRs were included in these evaluations. TtPD was measured from the dates of randomization until disease progression or death, whichever came first, and survival was measured from the dates of randomization until death from any cause. If signs of disease progression were absent within the treatment period, one of the following dates was used as the end-of-time interval: the date of the first documented sign of disease progression within the follow-up period or the date of death, provided that the clinical

diagnosis or postmortem examination had not indicated that the death was related to the study drug or resulted from a cause not related to study disease.

All patients who received at least two treatment cycles and who developed rapid tumor progression after one cycle were considered assessable for response. All patients who received at least one dose of study drug were assessable for toxicity. Thus, intent-to-treat analysis was not used for response and toxicity evaluation. All randomized patients were considered assessable for TtPD and OS.

Statistical Considerations

A total of 192 events were required to provide at least 80% power to be able to detect a hazard ratio of 1.50 between the two treatment arms for a two-sided test with an $\alpha = .05$. This corresponded to a median TtPD (primary end point) of 12 months in the GET arm with 80% power if the median TtPD for the reference group (FEC) was 8 months. Thus, a 50% improvement in TtPD was targeted. It was expected that 260 randomized patients (130 patients per arm) would be needed, assuming an accrual period of 18 months with a 12-month follow-up period.

Pretreatment characteristics were compared using the Fisher's exact and Wilcoxon rank sum tests. TtPD, survival, and duration of response were described by Kaplan-Meier estimates and subjected to a two-sided log-rank test for the null hypothesis of equal hazard rates. RRs and incidences of toxicities were compared using Fisher's exact test. All comparisons were performed at an $\alpha = .05$ (two-sided); 95% CIs for time-to-event measures were calculated according to the Brookmeyer and Crowley method.

TtPD and OS were subjected to Cox proportional hazards regression model using the predefined stratification factors of prior chemotherapy (adjuvant v none), age (≤ 53 years v > 53 years), menopausal status (premenopausal v postmenopausal), performance status (ECOG of 0 or 1 v 2), and prior adjuvant chemotherapy, prior hormonal therapy, prior radiotherapy, liver metastases, lung metastases, lymph node metastases, and bone metastases (presence v absence). In the event of nonproportionality of certain factors, time-dependent transformations were investigated.

RESULTS

Patient Characteristics

Between October 1999 and November 2002, 259 patients were enrolled onto the study, which comprised 29 centers in 12 countries; 124 patients were randomly

assigned to GET, and 135 were assigned to FEC. Most patients were diagnosed with ductal breast carcinoma (GET, 76%; FEC, 79%). The median disease-free interval from initial early breast cancer diagnosis to MBC was 3.9 years (range, 0.1 to 21.1 years) and 4.3 years (range, 0.5 to 17.8 years) for GET and FEC patients, respectively. Other baseline characteristics, including age, ECOG performance status, metastatic sites, receptor status, and prior therapy, were well balanced across treatment arms (Table 1). The only significant demographic difference between treatment arms was found for menopausal status; a higher percentage of premenopausal patients were randomly assigned to the FEC arm compared with the GET arm (28% v 15%, respectively; $P = .024$).

Table 1. Patient Characteristics

Characteristic	GET (n = 124)		FEC (n = 135)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	53		54	
Range	29-74		32-74	
Disease-free interval, years				
Median	3.9		4.3	
Range	0.5-21.1		0.5-17.8	
ECOG performance status				
0	63	50.8	61	45.2
1	52	41.9	64	47.4
2	9	7.3	10	7.4
Menopausal status				
Premenopausal	18	14.5	38	28.1*
Menopausal	8	6.5	5	3.7
Postmenopausal	96	77.4	91	67.4
Unknown	2	1.6	1	0.7
Metastatic sites				
Liver	76	61.3	66	48.9
Lung	49	39.5	64	47.4
Bone	45	36.3	50	37.0
Lymph node	38	30.6	48	35.6
Breast	18	14.5	28	20.7
Other†	55	44.4	57	42.2
≥ 3 organs involved	40	32.3	47	34.8
Receptor status				
ER positive	45	36.3	54	40.0
PR positive	34	27.4	41	30.4
ER negative	39	31.5	41	30.4
PR negative	49	39.5	49	36.3
Prior adjuvant chemotherapy	66	53.2	67	49.6
Prior hormonal therapy	52	41.9	47	34.8

Abbreviations: GET, gemcitabine, epirubicin, paclitaxel; FEC, fluorouracil, epirubicin, paclitaxel; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor.
*Significantly higher percentage of patients on the FEC versus GET arm ($P = .024$), as determined by the Fisher's exact test (two-sided at a $P = .05$ level of significance).
†Includes effusions/serious membrane, skin, abdomen, adrenal, axillary, bone marrow, chest, chest wall, eye, hilar, kidney not otherwise specified, mediastinum, neck, and ovary.

Exposure to Study Treatment

A total of 124 patients on the GET arm and 132 patients on the FEC arm received study drug for a total of 751 and 842 cycles, respectively. The median number of cycles per patient was seven (range, one to eight cycles) for GET and eight (range, one to eight) for FEC. After cycle 1, dose delays (defined as treatment postponed beyond day 23) occurred in 22.2% of cycles and in 56.1% of patients receiving GET versus in 20.4% of cycles and in 48.4% of patients receiving FEC ($P = .246$). Only 4.1% of cycles for GET and 2.3% of cycles for FEC were delayed more than 7 days. Significantly more dose reductions occurred on the GET arm compared with the FEC arm (8.0% of cycles and 36% of patients v 2.7% of cycles and 14.3% of patients, respectively; $P < .001$). Hematologic toxicity was the primary reason for dose delays and reductions. Relative dose-intensities were 89.7% for gemcitabine, 90.9% for epirubicin, and 91.4% for paclitaxel on the GET arm and 95.5% for FU, 94.0% for epirubicin, and 94.2% for cyclophosphamide on the FEC arm.

Primary Objective: TtPD

Estimates of median TtPD were 9.1 months (95% CI, 7.6 to 11.0 months) for GET and 9.0 months (95% CI, 6.6 to 10.3 months) for FEC, with median follow-up times of 21.6 and 19.2 months, respectively. There was no significant difference between arms in overall TtPD (Fig 2) as indicated by the log-rank P value of .557; the numbers of censored events for GET and FEC were 23 (18.6%) and 27 (20.5%), respectively. Multivariate Cox modeling analysis for TtPD showed that the hazard ratio for GET versus FEC was 0.9 (95% CI, 0.68 to 1.19; $P = .458$), indicating a similar risk of progression at any time point for patients on both treatment arms. The imbalance of menopausal status across arms at baseline did not have any significant impact on TtPD, as indicated by the results of the univariate analysis ($P = .487$).

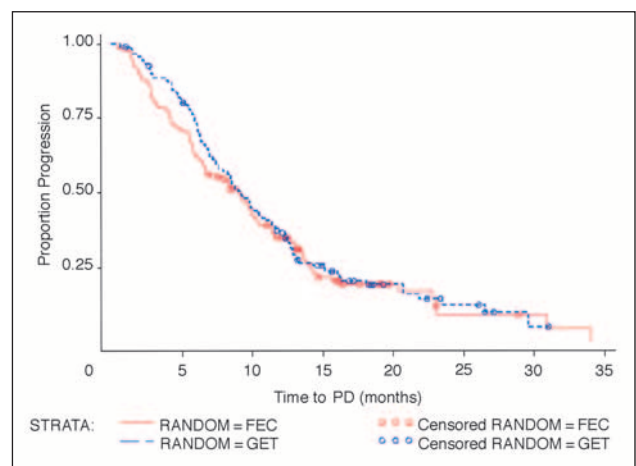


Fig 2. Kaplan-Meier curve for time-to-progressive disease (PD). FEC, fluorouracil, epirubicin, and paclitaxel; GET, gemcitabine, epirubicin, and paclitaxel.

Table 2. Best Response

Response	Assessable GET Patients (n = 114)		Assessable FEC Patients (n = 129)	
	No.	%	No.	%
Overall response*	71	62.3	66	51.2
95% CI, %	52.7 to 71.2		42.2 to 60.1	
Complete response	11	9.6	7	5.4
Partial response	60	52.6	59	45.7
Stable disease	34	29.8	47	36.4
Progressive disease	4	3.5	11	8.5
Not assessable†	5	4.4	5	3.9
Time to response, months‡				
Median	1.6		1.9	
95% CI	1.5 to 2.4		1.4 to 2.8	
Duration of response, months§				
Median	7.8		8.5	
95% CI	6.1 to 9.6		7.4 to 12.3	

Abbreviations: GET, gemcitabine, epirubicin, paclitaxel; FEC, fluorouracil, epirubicin, paclitaxel.
* $P = .093$.
†Best response not determined because of lack of follow-up data.
‡ $P = .407$.
§ $P = .125$.

Response

A total of 243 patients (GET, 114 patients; FEC, 129 patients) were assessable for response. The overall response rate (ORR) was 62.3% in the patient group receiving GET compared with 51.2% for patients receiving FEC, with a CR rate of 9.6% versus 5.4%, respectively, which was not statistically significant ($P = .093$; Table 2). In addition, median time to response and duration of response (Table 2) were not statistically different between treatment arms.

Survival

The estimated median OS did not differ significantly ($P = .61$), with OS times of 29.5 months for GET and 24.9 months for FEC. Because 60% of the events were censored, the 95% CIs for median survival were not estimated. Thus, survival data were not mature at the time of this analysis.

Table 3. WHO Grade 3 or 4 (worst grade) Hematologic Toxicity

Toxicity*	GET Patients (n = 123)				FEC Patients (n = 130)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Neutropenia	25	20.3	89	72.4	40	30.8	69	53.1
Thrombocytopenia	23	18.7	12	9.8	3	2.3	1	0.8
Anemia	24	19.5	2	1.6	8	6.2	2	1.5

Abbreviations: GET, gemcitabine, epirubicin, paclitaxel; FEC, fluorouracil, epirubicin, paclitaxel.
*Significant difference between arms in grades 3 and 4 toxicities combined per Fisher's exact test (two-sided); $P = .001$ for neutropenia and $P < .001$ for thrombocytopenia and anemia.

Table 4. WHO Grade 3 or 4 (worst grade) Nonhematologic Toxicity

Toxicity	GET (n = 130)		FEC* (n = 122)	
	No.	%	No.	%
Alopecia	81	66.4	81	62.3
Nausea and vomiting	16	13.1	23	17.7
Mucositis†	16	13.1	1	0.8
Allergy‡	9	7.4	0	0
Neurosensory toxicity‡	6	4.9	0	0
Hepatic toxicity‡	5	4.1	4	3.1
Diarrhea	5	4.1	1	0.8
Cardiotoxicity§	4	3.3	4	3.1
Skin rashes	4	3.3	0	0

Abbreviations: GET, gemcitabine, epirubicin, paclitaxel; FEC, fluorouracil, epirubicin, paclitaxel.
*FEC: n = 122 for all toxicities except hepatic toxicity, in which n = 120.
†Significant difference between arms in grade 3 or 4 toxicity per Fisher's exact test (two-sided); $P < .001$ for oral toxicity (grade 3 only), $P = .001$ for allergic toxicity, and $P = .012$ for peripheral neurotoxicity.
‡Includes alkaline phosphatase, bilirubin, and transaminases.
§Includes cardiac dysfunction, including pericarditis and cardiac rhythm disturbance.

Toxicity

A total of 123 patients with 749 treatment cycles in the GET arm compared with 130 patients with 830 treatment cycles in the FEC arm were assessable for the toxicity evaluation. Six patients were excluded from the toxicity evaluation; four patients (FEC, n = 3; GET, n = 1) did not receive study drug, and toxicity data were not available in two patients in the FEC arm.

Overall, no toxic deaths occurred. Hematologic and nonhematologic toxicities (grade 3 or 4) are listed in Tables 3 and 4, respectively. Neutropenia was the predominant grade 3 to 4 toxicity and was reported in 93% of the patients on the GET arm versus 84% of the patients on the FEC arm ($P = .001$). Febrile neutropenia occurred in 12.3% of the GET patients versus 2.7% of the FEC patients ($P = .003$). There were no episodes of life-threatening sepsis in either arm. Two patients on the FEC arm had major bleeding episodes, whereas no bleeding was observed in patients on the GET arm. With respect to nonhematologic toxicities (Table 4), significant differences between arms in incidences of grade 3 to 4 toxicities were noted for mucositis (grade 3 only, 13% for GET v 1% for FEC, $P < .001$), allergy (7% for GET v 0% for FEC, $P = .001$), and neurosensory toxicity (grade 3 only, 5% for GET v 0% for FEC, $P = .012$). For both treatment arms, similar frequencies were reported for alopecia, nausea and vomiting, hepatic toxicity, diarrhea, and cardiotoxicity.

DISCUSSION

This phase III trial failed to demonstrate superiority of the GET regimen compared with the FEC regimen in MBC

patients, as illustrated by a similar median TtPD of 9.1 and 9.0 months, respectively. In addition, ORR did not differ significantly between the two treatment arms (62.3% for GET *v* 51.2% for FEC).

Although the prognosis of the patients in our study was generally poor, the baseline factors indicative of a poor prognosis, such as the presence and extent of visceral metastases, were well balanced across treatment arms. The only factor that showed an imbalance across treatment arms was menopausal status because patients were not stratified by this factor. Although more premenopausal patients were randomly assigned to FEC than GET (28% *v* 15%, respectively), the univariate analysis indicated that this imbalance had no impact on the primary study end point of TtPD ($P = .487$).

The desired outcome of the current study, which was to show the superiority of TtPD with GET over FEC, was based on results achieved with the GET combination in a phase II trial that produced a 92% ORR.¹⁶ Accordingly, we designed our study such that the administration of GET would result in a TtPD of 12 months for GET and 8 months for FEC, with a power to detect a difference between arms of 80%. The shorter than expected median TtPD for GET of 9.1 months in the current phase III study may actually reflect a more realistic treatment effect than that projected from the results of the single-institution phase II study of highly selected patients. Furthermore, TtPD was superior than initially anticipated in the FEC arm. Moreover, the high relative dose-intensities found in both arms (91% for GET arm and 95% for FEC arm) underscore the feasibility and comparability of the regimens.

The present results should be interpreted within the context of the seven other randomized phase III trials of taxane-based chemotherapy in MBC patients,^{10-14,19,20} which have compared anthracycline-taxane combinations to standard anthracycline-based combinations as first-line chemotherapy for MBC patients. None of these trials showed a 12-month progression-free survival, which represented the primary objective in the present study. Four^{10,12,13,19} of these seven randomized phase III trials investigated paclitaxel-based regimens compared with combinations containing doxorubicin^{10,13} and epirubicin.^{12,19} ORRs, TtPD, and OS favored the paclitaxel-containing arm in one trial.¹⁰ Within these mentioned four trials, ORR and median TtPD ranged from 46%¹² to 68%¹⁰ and 6¹³ to 9.8 months,¹² respectively, in MBC patients receiving the paclitaxel-containing chemotherapy. This is comparable to the ORR of 62% and the median TtPD of 9.1 months in patients receiving the GET regimen in the present trial. With respect to patients randomly assigned to the anthracycline-based control regimen, ORR ranged from 41%¹² to 56%,¹⁹ which is again comparable to the 51% ORR for patients treated with FEC in the present study. In contrast, median TtPD ranged from 6¹³ to 8 months,¹² which is at least 1 month shorter compared with the median

TtPD of 9 months in patients receiving the FEC regimen in our present study. In any case, the present study was not powered to detect small differences between arms. Three phase III trials compared docetaxel-based regimens with combinations containing doxorubicin^{11,14} and epirubicin²⁰ as first-line treatment in MBC patients. ORR and TtPD significantly favored the docetaxel-containing arm in all of these trials.^{11,14,20} ORR and TtPD ranged from 55%¹¹ to 65%²⁰ and 7.2¹¹ to 9.3 months,¹⁴ respectively, in MBC patients receiving the docetaxel-containing chemotherapy compared with 37%²⁰ to 47%¹⁴ and 6.8¹¹ to 8 months,¹⁴ respectively, in patients treated with the anthracycline-containing control regimen.

The addition of gemcitabine as a third chemotherapeutic agent to the epirubicin-paclitaxel combination did not translate into a significant increase in grade 3 to 4 neutropenic episodes (93% of patients) compared with the doublet combinations of paclitaxel-doxorubicin or paclitaxel-epirubicin in similar trials (89% of patients).^{10,13} In contrast, grade 3 to 4 thrombocytopenia occurred in almost 29% of patients treated with GET in the current study compared with 2% and 7% of patients treated with doxorubicin and paclitaxel doublets, respectively.^{10,13} However, thrombocytopenia did not constitute a clinical problem for the GET-treated patients in our study because there were no bleeding episodes. This is in contrast to the FEC arm, in which two patients had bleeding events. Grade 3 to 4 anemia occurred in 21% of patients treated with GET compared with 9% of patients treated with the paclitaxel-doxorubicin doublet.¹⁰ Although nonhematologic grade 3 to 4 toxicities, including stomatitis and peripheral neuropathy, occurred significantly more often on the GET arm compared with the FEC arm, the incidences were similar to those seen in patients treated with a paclitaxel-doxorubicin doublet.¹³ However, it is worth emphasizing that cardiotoxicity did not constitute a major problem in the present trial overall and in patients receiving GET treatment in particular.

Considering our observations of a numerical but non-significant increase in ORR and CR and no improvement in TtPD with the GET regimen and the fact that these results are similar to those obtained with other taxane-based chemotherapy regimens, it is reasonable to assume that a plateau of activity might have been reached for currently available cytotoxic agents in the treatment of MBC. If this is the case, it may further strengthen the argument for sequential rather than concomitant use of cytotoxic agents in the treatment of this disease. This hypothesis was already tested in a phase III trial, where the combination therapy of paclitaxel and doxorubicin in MBC patients did not improve either survival or quality of life compared with sequential single-agent therapy.²¹ Moreover, within an accompanying editorial to this phase III trial,²² the sequential approach in MBC patients is rather advocated because combination therapy failed to contribute a meaningful benefit within this

trial. In any case, our present study was not powered to detect small differences between arms in ORR and OS. In addition, we have to consider the limited value of ORR as an end point in MBC studies. Because guidelines for cross-over therapy or information on subsequent therapy in the present patient cohort are lacking, the value of OS is also quite difficult to ascertain.

Assuming anthracycline-based chemotherapy still remains the state of the art treatment for anthracycline-naïve MBC patients, effective treatment options, such as docetaxel-capecitabine²³ or paclitaxel-gemcitabine,²⁴ have emerged for the treatment of anthracycline-pretreated MBC. However, the lack of cross-over use of single-agent capecitabine²³ or single-agent gemcitabine²⁴ in the majority of patients experiencing progressive disease under single-agent docetaxel²³ or single-agent paclitaxel²⁴ casts doubt on the superiority of the respective doublet. Conversely, recent results with docetaxel, doxorubicin, and cyclophosphamide in the adjuvant setting indicate that docetaxel-based triplet therapy might be of value in patients with early-stage breast cancer.²⁵ Within this context of a concomitant triple-regimen approach, the GET regimen was also administered in a neoadjuvant early breast cancer setting within an early phase II trial,²⁶ the definite value of which is premature to assess.

Acknowledgment

We thank the patients who are participating in the present trial and those listed in the Appendix.

Appendix

The following Central European Cooperative Oncology Group staff and main investigators participated in the trial: staff: Irmgard Resch, Margit Landsgesell, and Dagmar Just; Clinical Research Organization: International Electronic Monitoring (IEM); data management: InnoPharm, Smolensk, Russia; main investigators (in alphabetical order): Bulgaria: Antoaneta

Tomova, Regional Oncological Inpatient Dispensary, Plovdiv; Czech Republic: Lubos Petruzelka, Department of Oncology, Charles University, Prague; Milan Kuta, Department of Oncology and Radiotherapy, Hospital Chomutov, Chomutov; Hungary: Miklos Wenczl, Department of Oncoradiology, Markusovszky Teaching Hospital, Szombathely; Tamás Pintér, Department of Oncoradiology, Petz Aladár County Hospital, Győr; Israel: Adi Shani, Oncology Department, Kaplan Medical Center, Rehovot; Poland: Jacek Jassem, Medical University, Gdansk; Jerzy Zaluski, Department of Chemotherapy, Great Poland Cancer Center, Poznan; Jerzy Tujakowski, Regional Oncology Center, Bydgoszcz; Slovakia: Ivan Koza, National Cancer Institute, Bratislava; Turkey: Ugur Yilmaz, Faculty of Medicine, Department of Medical Oncology, University Izmir, Izmir; Erkisi Melek, Faculty of Medicine, Department of Medical Oncology, Cukurova University Adana, Adana; Günel Nazan, Faculty of Medicine, Department of Medical Oncology, Gazi University Ankara, Ankara; Nil Molinas Mandel, Department of Medical Oncology, Cerahpa a Medical School, Istanbul University, Istanbul; and Manavoglu Osman, Department of Medical Oncology, Faculty of Medicine, Uluda University Bursa, Bursa.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Consultant/Advisory Role: Christoph Zielinski, Amgen, Bio Life Science, Eli Lilly, Merck. Stock Ownership: Christoph Zielinski, Bio Life Science. Honoraria: Thomas Brodowicz, Eli Lilly. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

REFERENCES

1. Bray F, Sankila R, Ferlay J, et al: Estimates of cancer incidence and mortality in Europe in 1995. *Eur J Cancer* 38:99-166, 2002
2. Mettlin C: Global breast cancer mortality statistics. *CA Cancer J Clin* 49:138-144, 1999
3. Greenberg PA, Hortobagyi GN, Smith TL, et al: Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 14:2197-2205, 1996
4. Falkson G, Tormey DC, Carey P, et al: Long-term survival of patients treated with combination chemotherapy for metastatic breast cancer. *Eur J Cancer* 27:973-977, 1991
5. Fossati R, Confalonieri C, Torri V, et al: Cytotoxic and hormonal treatment for metastatic breast cancer: A systematic review of published randomized trials involving 31,150 women. *J Clin Oncol* 16:3439-3460, 1998
6. Italian Multicentre Breast Study with Epirubicin: Phase III randomized study of fluorouracil, epirubicin, and cyclophosphamide v fluorouracil, doxorubicin, and cyclophosphamide in advanced breast cancer: An Italian multicentre trial. *J Clin Oncol* 6:976-982, 1988
7. French Epirubicin Study Group: A prospective randomized phase III trial comparing combination chemotherapy with cyclophosphamide, fluorouracil, and either doxorubicin or epirubicin. *J Clin Oncol* 6:679-688, 1988
8. Gianni L, Munzone E, Capri G, et al: Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: High antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J Clin Oncol* 13:2688-2699, 1995
9. Dombrowsky P, Gehl J, Boesgaard M, et al: Doxorubicin and paclitaxel, a highly active combination in the treatment of metastatic breast cancer. *Semin Oncol* 23:23-27, 1996 (5 suppl 1)
10. Jassem J, Pienkowski T, Pluzanska A, et al: Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: Final results of a randomized phase III multicenter trial. *J Clin Oncol* 19:1707-1715, 2001
11. Mackey JR, Paterson A, Dirix LY, et al: Final results of the phase III randomized trial comparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) to FAC as first line chemotherapy (CT) for patients (pts) with metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 21:35a, 2002 (abstr 137)
12. Luck H, Thomssen C, Untch M, et al: Multicentric phase III study in first line treatment of advanced metastatic breast cancer (ABC): Epirubicin/paclitaxel (ET) vs epirubicin/cyclophosphamide (EC)—A study of the AGO Breast Cancer Group. *Proc Am Soc Clin Oncol* 19:73a, 2000 (abstr 280)

- 13.** Biganzoli L, Cufer T, Bruning P, et al: Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 multicenter phase III trial. *J Clin Oncol* 20:3114-3121, 2002
- 14.** Nabholz JM, Falkson C, Campos D, et al: Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: Results of a randomized, multicenter, phase III trial. *J Clin Oncol* 21:968-975, 2003
- 15.** Fogli S, Danesi R, Gennari A, et al: Gemcitabine, epirubicin and paclitaxel: Pharmacokinetic and pharmacodynamic interactions in advanced breast cancer. *Ann Oncol* 13:919-927, 2002
- 16.** Conte PF, Gennari A, Donati S, et al: Gemcitabine plus epirubicin plus Taxol (GET) in advanced breast cancer: A phase II study. *Breast Cancer Res Treat* 68:171-179, 2001
- 17.** Seidman AD: Monotherapy options in the management of metastatic breast cancer. *Semin Oncol* 30:6-10, 2003
- 18.** Pocock SJ, Simon R: Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 31:103-115, 1975
- 19.** Carmichael J: UKCCCR trial of epirubicin and cyclophosphamide (EC) vs epirubicin and Taxol (ET) in the first line treatment of women with metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 20:22a, 2001 (abstr 884)
- 20.** Bonnetterre J, Dieras V, Tubiana-Hulin M, et al: Six cycles of epirubicin/docetaxel (ET) versus 6 cycles of 5FU epirubicin/cyclophosphamide (FEC) as first line metastatic breast cancer (MBC) treatment. *Proc Am Soc Clin Oncol* 20:42a, 2001 (abstr 163)
- 21.** Sledge GW, Neuberg D, Bernardo P, et al: Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An intergroup trial (E1193). *J Clin Oncol* 21:588-592, 2003
- 22.** Seidman AD: Sequential single-agent chemotherapy for metastatic breast cancer: Therapeutic nihilism or realism? *J Clin Oncol* 21:577-579, 2003
- 23.** O'Shaughnessy J, Miles D, Vukelja S, et al: Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. *J Clin Oncol* 20:2812-2823, 2002
- 24.** O'Shaughnessy J, Nag S, Calderillo-Ruiz G, et al: Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first-line treatment for anthracycline pre-treated metastatic breast cancer (MBC): Interim results of a global phase III study. *Proc Am Soc Clin Oncol* 22:7, 2003 (abstr 25)
- 25.** Nabholz JM, Pienkowski T, Mackey J, et al: Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (BC) patients: Interim analysis of the BCIRG 001 study. *Proc Am Soc Clin Oncol* 21:36a, 2002 (abstr 141)
- 26.** Conte PF, Gennari A, Santoto A, et al: Induction chemotherapy in operable breast cancer: A multicenter Italian phase II study with the GET regimen. *Proc Am Soc Clin Oncol* 22:35, 2003 (abstr 140)