VOLUME 23 · NUMBER 13 · MAY 1 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Vinorelbine Plus Cisplatin Versus Docetaxel Plus Gemcitabine in Advanced Non–Small-Cell Lung Cancer: A Phase III Randomized Trial

Vassilis Georgoulias, Alexandros Ardavanis, Xanthi Tsiafaki, Athina Agelidou, Penelope Mixalopoulou, Ourania Anagnostopoulou, Panagiotis Ziotopoulos, Michael Toubis, Kostas Syrigos, Nikolaos Samaras, Aris Polyzos, Anna Christou, Stylianos Kakolyris, Charalambos Kouroussis, Nikolaos Androulakis, George Samonis, and Dora Chatzidaki

From the Department of Medical Oncology, University General Hospital, Heraklion, Crete; 1st Department of Medical Oncology, Agios Savas Anticancer Hospital, Athens; 1st and 2nd Departments of Pulmonary Diseases, Sismanoglio General Hospital, Athens; 1st, 3rd, 6th, 7th, and 8th Departments of Pulmonary Diseases; Medical Oncology Unit; 3rd Department of Internal Medicine of University of Athens, Sotiria General Hospital, Athens; 2nd Department of Pulmonary Diseases, Papanicolaou General Hospital, Thessaloniki; Medical Oncology Unit, Department of Propedeutic Medicine of University of Athens, Laiko General Hospital, Athens, Greece.

Submitted April 5, 2004; accepted September 24, 2004.

Supported in part by a research grant From the Cretan Association for Biomedical Research (CABR).

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

Address reprint requests to Vassilis Georgoulias MD, PhD, Department of Medical Oncology, University General Hospital of Heraklion, PO Box 1352, 711 10 Heraklion, Crete, Greece; e-mail: georgoul@med.uoc.gr.

0732-183X/05/2313-2937/$20.00

DOI: 10.1200/JCO.2005.04.016

ABSTRACT

Purpose
To compare the activity and tolerability of docetaxel/gemcitabine (DG) and vinorelbine/cisplatin (VC) combinations in chemotherapy-naïve non–small-cell lung cancer (NSCLC) patients.

Patients and Methods
Patients with advanced NSCLC were randomly assigned to receive either DG (gemcitabine 1,000 mg/m^2 [days 1 and 8] plus docetaxel 100 mg/m^2 [day 8]) or VC (vinorelbine 30 mg/m^2 [days 1 and 8] plus cisplatin 80 mg/m^2 [day 8]) and prophylactic recombinant human granulocyte colony-stimulating factor (150 μg/m^2 subcutaneously [day 9 through 15]) every 3 weeks.

Results
A total of 413 randomly assigned patients were analyzed for response and toxicity (DG, n = 197; VC, n = 192). Median survival was 9.0 and 9.7 months (P = .965) for DG and VC arms, respectively; the corresponding 1-year survival rates were 34.3% and 40.8%, respectively. Overall response rate was 30% (95% CI, 23.9% to 36.3%) and 39.2% (95% CI, 32.5% to 45.9%; P = .053) for DG and VC, respectively. Toxicity was as follows (DG *v* VC): grade 2 to 4 anemia, 34% *v* 55% (P = .0001); grade 3 to 4 neutropenia, 16% *v* 37% (P = .0001); febrile neutropenia, 6% *v* 11% (P = .009); and grade 3 to 4 nausea and vomiting, 1% *v* 15% (P = .003). Nephrotoxicity occurred in 8% and ototoxicity in 2% of VC-treated patients. There were five and six treatment-related deaths in the DG and VC arms, respectively. Quality of life was improved in DG but not in VC patients.

Conclusion
Although the two regimens produced comparable overall survival, the DG regimen had a better toxicity profile. Therefore, DG could be used in the first-line setting of advanced NSCLC, especially for patients who cannot tolerate cisplatin.

J Clin Oncol 23:2937-2945. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Lung cancer is one of the most common malignancies worldwide[1] and the leading cause of cancer-related deaths in Western countries.[2,3] Non–small-cell lung cancer (NSCLC) accounts for approximately 80% of cases, and only a third of patients present with resectable disease at diagnosis. Without treatment, less than 10% of patients survive for 1 year, and median survival is 5 to 6 months.[1] Cisplatin-based chemotherapy is associated with improved response rates and survival benefit compared with noncisplatin regimens.[4,5] Moreover, cisplatin treatment is an independent predictor of survival.[6] Therefore, platinum-based chemotherapy regimens

are considered the gold standard for first-line treatment of advanced NSCLC.

Cisplatin-related severe nausea and vomiting, renal toxicity, ototoxicity, and neuropathy limit its therapeutic ratio. Several drugs with novel mechanisms of action and significant activity in NSCLC have been developed, including paclitaxel, docetaxel, vinorelbine, gemcitabine.[7] Combinations of these drugs with cisplatin have achieved objective responses up to 50%, median survival up to 14.2 months, and 1-year survival rates up to 54%.[8-14] However, although some platinum-containing regimens have produced clinically meaningful benefits in NSCLC, there is no evidence that one platinum-containing regimen is overwhelmingly superior.[13-18]

The combination of vinorelbine plus cisplatin (VC) is a frequently used first-line regimen in advanced NSCLC, with objective responses ranging from 24.5% to 44% and a median survival of 8.0 to 9.2 months; however, this regimen has considerable toxicity.[13,16-18] Docetaxel plus gemcitabine (DG) is also an active and well-tolerated combination in NSCLC.[19-20] Although, comparisons of chemotherapy doublets incorporating newer drugs have demonstrated no differences in terms of overall survival between the platinum- and non–platinum-based regimens, nonplatinum combinations have a more favorable toxicity profile.[21-23]

Prolonging survival and improving tumor-related symptoms and/or quality of life are the main objectives of palliative chemotherapy in advanced NSCLC. Therefore, chemotherapy-related toxicity is an important consideration. Nonplatinum regimens conferring a similar survival benefit to platinum-based chemotherapy could be a valuable therapeutic alternative for patients with advanced NSCLC. The Lung Cancer Working Group of the Hellenic Oncology Research Group (HORG) conducted a prospective, multicenter, randomized phase III trial to compare the activity and tolerability of VC and DG in advanced NSCLC.

PATIENTS AND METHODS

Patients

Eligible patients were chemotherapy-naïve, 18 to 75 years of age, with histologically or cytologically confirmed inoperable stage IIIB (with pleural effusion) or stage IV NSCLC. Additional inclusion criteria included a WHO performance status (PS) of 0 to 2; at least one bidimensionally measurable lesion outside an irradiation field; absence of a second primary tumor except for basal cell carcinoma of the skin or carcinoma-in-situ of the cervix; adequate bone marrow, kidney, and liver functions (with the exception of alkaline phosphatase, up to five times the upper limit of normal in patients with liver metastases); a negative pregnancy test in women of childbearing age; and a life expectancy $\geq$ 3 months. CNS metastases were allowed provided that they had been irradiated and were clinically and radiologically stable; prior radiotherapy was allowed provided that less than 25% of the total bone marrow had been irradiated and that treatment was completed at least 4 weeks before enrollment. Patients were excluded for severe cardiopulmonary insufficiency, severe uncontrolled angina pectoris, myocardial infarction within 6 months before enrollment, active infection, or severe malnutrition (loss of $>$ 15% of body weight). All patients were required to provide written informed consent, and the study was approved by the ethics and scientific committees of each participating institution.

Treatment Plan and Dose Modifications

Eligible patients were centrally registered and stratified according to age, PS, and disease stage, and were randomly assigned to either DG (gemcitabine [Gemzar; Eli Lilly, Indianapolis, IN] 1,000 mg/m^2 as a 30-minute intravenous [IV] infusion on days 1 and 8 plus docetaxel [Taxotere; Aventis, Bridgewater, NJ] 100 mg/m^2 as a 1-hour IV infusion on day 8) or VC (vinorelbine [Navelbine; Pierre Fabre, Paris, France] 30 mg/m^2 as a 30-minute IV infusion on days 1 and 8 plus cisplatin [Platinol; Bristol Meyers Squibb, Princeton, NJ] 80 mg/m^2 on day 8). Recombinant human granulocyte colony-stimulating factor (rhG-CSF; 150 μg/m^2/d subcutaneously; Granocyte, Aventis) was given prophylactically to all patients on days 9 through 15. Chemotherapy cycles were repeated every 3 weeks. Docetaxel and vinorelbine were given before gemcitabine and cisplatin, respectively. Patients receiving DG were administered standard dexamethasone premedication (8 mg orally before and after docetaxel administration), as previously reported.[8-9] All patients received ondansetron and those receiving cisplatin were also administered 4 mg dexamethasone, adequate hydration, and forced diuresis. The DG regimen was administered on an outpatient basis, whereas most VC patients were admitted overnight for hydration.

Patients with evidence of progressive disease (PD) were withdrawn from the study; patients with stable disease (SD) received a maximum of six cycles; and patients with a complete response or partial response (PR) after the sixth cycle received 3 additional cycles.

Dose adjustments were based mainly on hematologic parameters. Doses of both drugs were reduced by 25% in subsequent cycles if chemotherapy-induced febrile neutropenia or grade 4 thrombocytopenia lasting for more than 5 days occurred; in the absence of fever, the doses of both drugs were reduced by 15%. The doses of vinorelbine, docetaxel, and cisplatin were reduced by 25% for grade 2 or 3 neurotoxicity. Dose reductions were maintained for all subsequent cycles. Patients requiring more than one dose reduction were withdrawn from the study.

Baseline and Follow-Up Assessments

Pretreatment evaluation included a complete medical history and physical examination (PE); a CBC with differential and platelet count; standard biochemical profile; ECG; chest radiographs; computed tomographic (CT) scans of the chest, abdomen, and brain; and a whole-body bone scan. During treatment, a CBC was performed weekly; in the event of grade 3 or 4 neutropenia, febrile neutropenia, or grade 4 thrombocytopenia, the CBC was repeated daily until the absolute granulocyte count was $\geq$ 1000/μL and the platelet count was $\geq$ 50,000/μL. A detailed medical history was taken and a complete PE with clinical neurological assessment was performed before each cycle of treatment to assess disease symptoms and treatment toxicity. Biochemical tests, ECG, and chest radiographs were done every 3 weeks. Patients with grade 3 or 4 neurotoxicity were evaluated by motor and sensory nerve conduction-velocity tests.

Lesions were measured after each cycle if assessable by physical examination or by chest radiograph; all patients were assessed for response by ultrasonography or CT scans after every three cycles of chemotherapy. Standard WHO toxicity and response criteria were used.[24] All objective responses, assessed by two independent radiologists, had to be maintained for at least 4 weeks.

The duration of response was calculated from the day of the first demonstration of response to disease progression; time to tumor progression (TTP) was calculated from study entry until the day of the first evidence of disease progression. Overall survival was measured from study entry to death. Tumor-related symptoms and quality of life (QoL) were evaluated and scored at baseline and before every cycle with the Lung Cancer Symptom Scale (LCSS) questionnaire.[25-27]

Statistical Analysis

The primary end point was overall survival; secondary end points were the overall response rate (ORR), TTP, and toxicity profile. Based on previous trials evaluating the VC[13] and DG[20] regimens, the present study was designed to detect a 4-month difference of overall survival with an 80% power at a significance level of .05. Three hundred sixty-two patients (181 per arm) were required in order to achieve the statistical hypothesis.[28] Although not included in the boundary criteria, separate subgroup analyses were planned according to disease stage, PS, and histology. All clinical data were held centrally (Clinical Trial Office, Department of Medical Oncology, University General Hospital of Heraklion, Crete, Greece) and analyzed (Department of Biostatistics, School of Medicine, University of Crete, Heraklion, Crete, Greece) using the SPSS (version 10.0) program.

Patients who received at least three chemotherapy cycles and those who received at least one cycle for toxicity were assessed for response. The actuarial survival was estimated using Kaplan-Meier curves, and the associated 95% CIs were calculated using Greenwood's formula.[29] The comparison of overall survival and TTP was assessed using the log-rank test. Quantitative factors were compared by Pearson's χ^2 contingency table analysis (or Fisher's test whenever appropriate); relative risks were estimated by the odds ratios (ORs).[28,30] The independent effect of treatment and other prognostic factors on the primary and secondary binary end points was analyzed by logistic regression,[29,30] and on survival and TTP by Cox's proportional hazards model.[28]

RESULTS

Patient Characteristics

Between April 1999 and September 2002, 413 chemotherapy-naïve patients with NSCLC from 31 institutions were enrolled (Appendix 1). Two hundred nine patients were randomly assigned to DG, and 204 to VC. Three patients died as a result of progressive disease before chemotherapy administration, whereas five patients refused treatment and four did not meet the entry criteria in the DG group. In addition, five patients refused treatment and seven did not meet the entry criteria in the VG group. All patients were included in the analysis of response, and 197 DG and 192 VC patients were assessable for toxicity. Table 1 presents baseline patient characteristics.

Table 1. Patient Characteristics

	Docetaxel/ Gemcitabine Arm		Vinorelbine/ Cisplatinum Arm	
	No. of Patients	%	No. of Patients	%
Patients randomly assigned	209		204	
Age, years				
Median	63		64	
Range	36-75		46-75	
Sex				
Male	186	89	179	88
Female	23	11	25	12
WHO performance status				
0	92	44	88	43
1	94	45	55	47
2	23	11	21	10
Histology				
Squamous	80	38	93	46
Adenocarcinoma	85	41	76	37
Large cell	12	6	4	2
Undifferentiated	30	14	31	15
Mixed	2	1	—	—
Stage				
IIIB	80	38	73	36
IV	129	62	131	64
Organ involvement				
Lung	194	99	198	98
Pleura	52	27	51	27
Lymph nodes	145	74	124	65
Liver	29	15	24	13
Adrenal	25	13	27	14
Bones	45	23	56	29
Brain	20	10	21	11
Other	16	9	21	1
Prior treatment				
Surgery	18	9	17	8
Radiotherapy	8	4	12	6
None	183	87	175	86

Survival

The median follow-up was 9.0 months (range, 0.5 to 43.4 months) for DG and 8.6 months (range, 0.5 to 38 months) for VC ($P = .837$). Two patients receiving DG and one receiving VC were lost to follow-up and were considered dead at the time of the last consultation.

At the time of this analysis, 156 DG patients (75%) and 145 VC patients (71%) had died ($P = .387$) as a result of the following: disease progression (DG, 143; VC, 132); treatment-related toxicity (DG, 5; VC, 6); and other reasons unrelated to the disease or treatment (DG, 8; VC, 4). The median overall survival was 9.0 months for DG and 9.7 months for VC (log-rank $P = .965$; Fig 1). The respective 1- and 2-year survival rates were 34.3% and 14.1% for DG and 40.8% and 11.3% for VC (Table 2). Survival was not affected by PS, disease stage, tumor histology, or response to treatment.

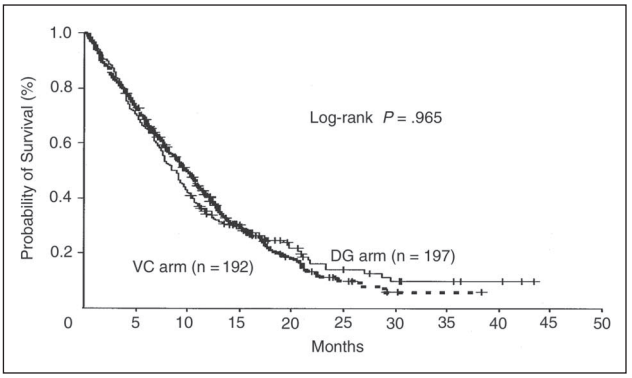

Fig 1. Patient survival Kaplan-Meier estimate of survival of patients treated with docetaxel/gemcitabine (DG) and vinorelbine/cisplatinum (VC) regimens.

For DG and VC combined, the median overall survival for patients with a PS of 0 to 1 and PS of 2 was 9.6 (95% CI, 8.5 to 10.7) and 5.5 months (95% CI, 3.1 to 8.0; log-rank $P = .020$), respectively. The median survival was 12.9 months (95% CI, 9.4 to 16.3) and 7.7 months (95% CI, 6.7 to 8.8; log-rank $P = .0001$) for stage IIIB and IV patients, respectively.

A proportional hazards regression analysis confirmed that response to chemotherapy and stage of disease had a significant effect on survival (hazard ratio [HR] = 1.954; 95% CI, 1.525 to 2.502; $P = .0001$; and HR = 1.807; 95% CI, 1.397 to 2.336; $P = .0001$, respectively), but chemotherapy regimen or histology did not. Conversely, PS had a marked but not statistically significant effect on the risk of death (HR = 1.380; 95% CI 0.961 to 1.982; $P = .081$).

Fifty-seven DG patients (29%) and 46 VC patients (24%) received second-line chemotherapy. The median overall survival for patients who did not receive second-line chemotherapy was 7.6 months for DG (range 0.5 to 43.0 months; n = 140) compared with 9.0 months (range 0.5-30.0 months; n = 146) for VC (log-rank $P = .499$).

Response to Treatment

The ORR for DG was 30% (1% CR + 29% PR), and 39.2% for VC (1.5% CR + 37.7% PR; $P = .053$; intention-to-treat analysis; Table 3). Logistic regression analysis revealed that treatment ($P = .040$) and stage of disease ($P = .013$), but not PS or tumor histology were independent predictive factors for response. Indeed, the risk of SD + PD for patients treated with DG was higher than for those treated with VC (OR = 1.553; 95% CI, 1.021 to 2.359). Similarly, the odds ratio of SD + PD for patients with stage IV disease was approximately 1.7 times higher than for patients with stage IIIB disease (OR = 1.714; 95% CI, 1.121 to 2.622).

The median duration of response was 5.0 and 6.0 months for DG and VC, respectively. The median TTP was 4.0 and 5.0 months for DG and VC, respectively (log-rank $P = .456$; Fig 2). The TTP was not affected by PS, stage of disease, or tumor histology.

Table 2. Survival Analysis in Assessable Patients

	DG Arm (n = 197)	VC Arm (n = 192)	P*
Overall Survival			
Median, months	9.0	9.7	.965
Range, months	0.5-43.4	0.5-38.4	
95% CI	7.7 to 10.2	8.3 to 11.2	
1 year, %	34.3	40.8	
2 year, %	14.1	11.3	

Abbreviations: DG, docetaxel/gemcitabine arm; VC, vinorelbine/cisplatinum arm.
*Log-rank test.

Treatment Compliance

A total of 829 DG and 810 VC cycles were administered with 88 DG patients (45%) and 76 VC patients (40%) receiving six or more cycles. The median number of cycles was four (range, one to nine) in both the DG and VC arms. The median interval between cycles was 22 days for both arms. Treatment was delayed in 190 DG cycles (23%) and 194 VC cycles (24%; $P = .664$) for hematologic (DG, 22 cycles; VC, 49 cycles; $P = .0001$) and nonhematologic (DG, 24 cycles; VC, 14 cycles; $P = .076$) toxicity. All other cycles were delayed for reasons unrelated to treatment or toxicity. Treatment delays of ≤ 7 days occurred in 87 DG cycles (10%) and 86 VC cycles (11%), and dose reductions were required in 62 DG cycles (8%) and 99 VC cycles (12%; $P = .001$).

The median administered dose-intensity was 30.6 mg/m^2/wk for docetaxel and 619 mg/m^2/wk for gemcitabine, corresponding to 93% and 93% of the protocol-planned dose, respectively. The median administered dose-intensity for vinorelbine was 18 mg/m^2/wk and 23 mg/m^2/wk for cisplatin, corresponding to 90% and 85% of the protocol-planned dose, respectively.

Toxicity

Safety was assessed in all patients who received at least one treatment cycle and in all cycles (Table 4). Overall, grade 2 to 4 anemia occurred in 67 DG patients (34%) and 105 VC patients (55%; $P = .0001$). Grade 3 to 4 neutropenia occurred in 32 patients (16%) and 71 patients (37%) treated with DG and VC, respectively ($P = .0001$).

Twelve DG patients (6%) and 21 VC patients (11%) developed febrile neutropenia ($P = .086$). All required hospital admission for antibiotic treatment and rhG-CSF; one DG patient and three VC patients died as a result of sepsis. Thirty-one DG cycles (4%), corresponding to 29 patients, and 93VC cycles (14%), corresponding to 52 patients required additional rhG-CSF ($P = .0001$).

Grade 3 to 4 nausea and vomiting was more frequent with VC than with DG (15% *v* 2%; $P = .0001$). Grade 2 to 4

Table 3. Response in Assessable Patients

	Docetaxel/Gemcitabine Arm (n = 209)		Vinorelbine/Cisplatinum Arm (n = 204)		
	No. of Patients	%	No. of Patients	%	*P*
Response					
CR	2	1	3	1.5	
PR	61	29	77	57.7	
SD	50	24	33	16	
PD	96	46	91	44.6	
Overall response rate, CR + PR					
Patients, %	30		39.2		.053*
95% CI	23.92 to 36.36		32.52 to 45.92		
Duration of response, months					
Median	5		6		.833†
Range	1-38		1-27		
Time to progression, months					
Median	4		5		.456†
Range	0.5-43		0.5-29		

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*Pearson's χ^2 test.
†Log-rank test.

neurotoxicity occurred more often with VC than with DG (26% *v* 15%; $P = .004$). In the VC arm, nephrotoxicity occurred in 15 patients (8%) and ototoxicity in three patients (2%). Nail disorders were observed only with DG (grade 2 to 3; 15%). Non-neutropenic infections developed in 37 DG patients (19%) and 29 VC patients (15%). Other toxicities were mild (Table 4). Overall, VC had significantly more toxicity than DG irrespective of PS (Table 5).

There were five treatment-related deaths in the DG arm: febrile neutropenia, n = 2; cardiac arrest, probably due to myocardial ischemia, n = 1; febrile pneumonitis, n = 1; and sepsis without neutropenia, n = 1. Six patients died in the VC arm: febrile neutropenia, n = 3; acute renal failure, n = 1, severe gastrointestinal bleeding due to grade 4 thrombocytopenia, n = 1; and sudden death of unknown etiology, n = 1.

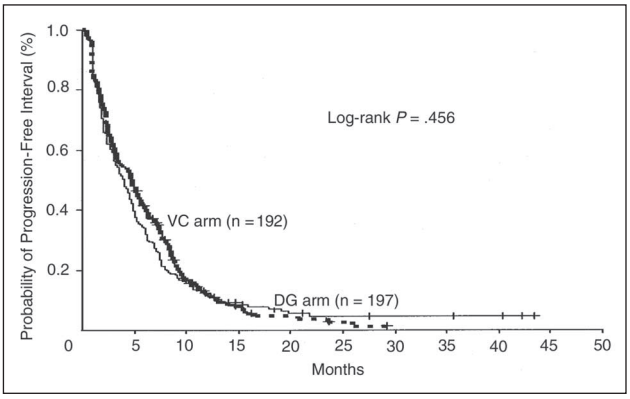

Fig 2. Patients' progression-free interval Kaplan-Meier estimate of progression-free interval of patients treated with docetaxel/gemcitabine (DG) and vinorelbine/cisplatiunum (VC) regimens.

Symptoms and QoL Assessment

Patients' compliance with QoL assessment for the DG arm was 90% at baseline, 88% at third cycle, and 96% at end of chemotherapy (EoC). Similarly, for VC arm, compliance was 88% at baseline and at third cycle, and 83% at EoC. Baseline assessment revealed that DG patients were scored higher than VC patients in terms of hemoptysis, (DG score = 1.9 *v* VC score = 0.89; $P = .035$) and total symptomatic distress (DG score = 4.88 *v* VC score = 3.35; $P = .027$). However, further analysis showed that there were no statistically significant differences between the two arms at third cycle and at EoC.

Patients treated with the DG regimen reported a significant improvement in QoL between baseline and EoC assessment for hemoptysis (score before chemotherapy = 1.99 *v* score after chemotherapy = 0.54; $P = .042$) and pain (score before chemotherapy = 3.46 *v* score after chemotherapy = 1.5; $P = .039$). On the contrary, patients treated with VC regimen experienced no significant improvement of QoL or tumor-related symptoms between baseline and EoL assessment.

DISCUSSION

This multicenter phase III randomized study demonstrated that a nonplatinum chemotherapy regimen (DG) has comparable efficacy to a platinum-based regimen (VC) in terms of overall survival in patients with advanced NSCLC.

Table 4. Hematologic and Nonhematologic Toxicity

Toxicity	Docetaxel/Gemcitabine Arm (n = 197)								Vinorelbine/Cisplatinum Arm (n = 192)								
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4		
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	*P*
Anemia	108	55	63	32	4	2	—		73	38	93	48	12	6	—		.0001*
Neutropenia	22	11	17	9	19	10	13	7	22	12	20	10	23	12	48	25	.0001†
Thrombocytopenia	66	34	9	5	3	2	3	2	49	26	4	2	5	3	5	3	.283†
Nausea/vomiting	14	7	8	4	1	1	1	1	19	10	30	16	21	11	7	4	.0001†
Diarrhea	13	7	12	6	7	4	3	2	13	7	4	2	4	2	1	1	.203
Mucositis	2	1	2	1	1	1	—		3	2	2	1	—		—		.674*
Neurotoxicity	24	12	18	9	7	4	3	2	35	18	28	15	20	10	2	1	.004*
Asthenia	61	31	22	11	12	6	—		41	21	36	19	19	10	—		.116†
Hypersensitivity reactions	8	4	5	3	2	1	—		1	1	3	2	—		—		.215*
Nail disorders	30	15	18	9	12	6	—		—		—		—		—		.001†
Nephrotoxicity	—		—		—		—		—		10	5	4	2	1	1	—
Ototoxicity	—		—		—		—		—		2	1	1	1	—		—
Hepatic	5	3	3	2	—		—		—		—		—		—		—
Pneumonitis	—		2	1	—		1	1	—		1	1	—		—		—

*Comparison of grade 2 to 3.
†Comparison of grade 3 to 4.

Indeed, the median overall survival was 9.0 and 9.7 months for patients treated with DG and VC, respectively. Moreover, the 1- and 2-year survival rates were 34.3% and 14.1% for DG and 40.8% and 11.3% for VC, respectively. Therefore, our trial could not demonstrate a 4-month survival difference of NSCLC patients treated with DG or VC regimens. However, overall survival of patients who did not receive second-line chemotherapy favored VC compared with DG (9.0 *v* 7.6 months, respectively), but this difference was not reach statistical significance. Multivariate analysis demonstrated that disease stage and response to treatment were independent prognostic factors for survival, irrespective of the regimen. As with survival, TTP was not different between the two arms and was not affected by PS, stage of disease, or tumor histology.

These observations are consistent with those of previous randomized studies, which demonstrated that nonplatinum-based chemotherapy doublets incorporating newer anticancer drugs have similar activity in terms of overall survival as corresponding platinum-based doublets. We have reported that there were no significant differences between docetaxel plus cisplatin and docetaxel plus gemcitabine in patients with advanced NSCLC in terms of objective response rate, median TTP, median overall survival,

Table 5. Grade 3 to 4 Toxicity According to Performance Status

	Performance Status 0 to 1					Performance Status 2				
	DG (n = 176)		VC (n = 173)			DG (n = 21)		VC (n = 19)		
	No. of Patients	%	No. of Patients	%	*P*	No. of Patients	%	No. of Patients	%	*P*
Anemia*	58	33	91	53	.0001	9	43	14	74	.049
Neutropenia	31	18	67	39	.0001	1	5	4	21	.120
Thrombocytopenia	6	3	8	5	.563	—		2	11	.127
Nausea/vomiting	2	1	23	13	.0001	—		5	26	.012
Diarrhea	8	5	5	3	.577	2	10	—		.168
Mucositis	1	1	—		.323	—		—		—
Neurotoxicity	8	5	16	9	.085	2	10	6	32	.082
Asthenia*	28	16	47	27	.120	6	29	8	42	.874
Nephrotoxicity	—		11	6	.001	—		4	21	.031
Ototoxicity	—		1	1	.319	—		—		—

Abbreviations: DG, docetaxel/gemcitabine arm; VC, vinorelbine/cisplatinum arm.
*Grade 2 to 3.

and 1-year survival.[21] Similarly, Kosmidis et al[22] did not show a significant difference in terms of median overall survival and 1-year survival between the paclitaxel plus carboplatin and paclitaxel plus gemcitabine chemotherapy regimens. A Spanish Cooperative Group[31] failed to find any difference in survival between gemcitabine plus cisplatin and the sequential doublets of gemcitabine plus vinorelbine and ifosfamide plus vinorelbine. Gridelli et al[23] found a 6-week higher median overall survival with cisplatin plus either gemcitabine or vinorelbine versus gemcitabine plus vinorelbine, but this difference did not reach statistical significance. A preliminary analysis of Eurpoean Organisation for Research and Treatment of Cancer (EORTC) trial 8975 showed a trend towards better overall survival in favor of the platinum-based regimens (cisplatin continued with either paclitaxel or gemcitabine) compared with a nonplatinum (paclitaxel/gemcitabine) combination.[32] Therefore, Schiller[33] concluded that third-generation non–platinum-based chemotherapy regimens, if not equivalent in terms of overall survival to the corresponding platinum-based doublets, are very close. A meta-analysis of updated survival data of all trials may more appropriately address whether there are differences between platinum- and non–platinum-based regimens.

Based on an intention-to-treat analysis, the ORR between the two arms marginally reached statistical significance ($P = .053$). Logistic regression analysis revealed that treatment and stage of disease were independent predictive factors for response. Previous studies comparing platinum- with non–platinum-based doublets in patients with advanced NSCLC also failed to reveal significant differences in response rate (21% to 23%, 31% to 32%). Moreover, a subgroup analysis of the Hellenic Cooperative Oncology Group (HECOG) trial showed that response rate was affected by PS, but not by disease stage, as was the case in our study.[22] This observation seems to indicate that different chemotherapy regimens have different activity in subgroups of NSCLC patients. This hypothesis is further supported by recent results of the Eastern Cooperative Oncology Group (ECOG) trial 1594, which showed that patients with a PS of 2 had a lower response rate, TTP, median survival (4.6 months), and 1-year survival than those with a PS of 0-1.[15]

In the present study, patients with PS of 2 were also enrolled because the trial was initiated in April 1999, when the impact of patients with PS of 2 on the response rate and the toxicity profile of different chemotherapy regimens was still unclear. However, the patients with PS of 2 represent only 10% and 11% of the enrolled DG and VC patients, respectively; this low proportion of patients with PS of 2 is unlikely to have an impact on response rate or TTP. Conversely, their survival was significantly lower then that of patients with PS of 0 to 1, as already it has been reported.[15, 22]

The VC regimen was associated with more severe myelosuppresion than DG, despite the prophylactic use of rhG-CSF. Although dose-density chemotherapy regimens with rhG-CSF support have not demonstrated any superiority over less myelotoxic chemotherapy combinations, we decided to administer prophylactically the growth factor for two main reasons: to decrease the known myelotoxicity of the VC regimen, and to use the DG combination at the same dose and schedule as it was already used in our previous studies.[20,21] The incidence of severe neutropenia and grade 2 to 4 anemia was significantly higher with VC than with DG. Moreover, the incidence of febrile neutropenia was significantly higher with VC than with DG, but fatal episodes were equally distributed between the two arms. The higher incidence of severe neutropenia observed in the VC arm required a higher and/or more prolonged use of rhG-CSF, increasing treatment cost. Finally, the severe myelotoxicity of VC had a severe impact on patients' compliance with treatment, as the number of delayed cycles due to hematologic toxicity was significantly higher with VC than with DG. Moreover, the incidence of cisplatin-related toxicities such as nausea and vomiting, nephrotoxicity, and ototoxicity were observed mainly with VC. Overall, DG was associated with a more favorable toxicity profile. Similar results in favor of the nonplatinum doublets have also been observed in previous studies.[21,23] In addition, QoL assessment showed that DG regimen significantly improved hemoptysis and pain after 6 cycles of chemotherapy; no such difference was observed in patients treated with VC regimen. Moreover, the comparison of the QoL between the two treatment arms revealed that, despite the fact that DG-treated patients scored higher in terms of hemoptysis and total symptomatic distress than VC-treated patients before chemotherapy, these differences were disappeared at EoC. These findings clearly indicate that the effect of DG regimen on QoL was higher than that of VC combination.

In conclusion, our observations show that despite the higher response rate obtained with VC than with DG, there was no difference between the two regimens in terms of survival. The more favorable toxicity profile of DG supports its use as first-line chemotherapy, especially in patients who cannot tolerate cisplatin and/or in patients with severe comorbitities or poor PS. However, the higher cost of the DG regimen is an issue that should be taken into account for the final therapeutic decision.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Appendix. Participating Institutions and Investigators

Institution	Investigator(s)
Department of Medical Oncology, University General Hospital of Heraklion, Crete	V. Georgoulias, S. Kakolyris, C. Kouroussis, N. Androulakis, G. Samonis
Department of Pulmonary Diseases, University General Hospital of Heraklion, Crete	D. Bouros
Department of Medical Oncology, Venizelion General Hospital of Heraklion, Crete	S. Tsousis
Department of Pulmonary Diseases, Venizelion General Hospital of Heraklion, Crete	N. Bachlitzanakis
1st Department of Medical Oncology, Agios Savas Anticancer Hospital of Athens	A. Ardavanis, A. Alexopoulos
2nd Department of Medical Oncology, Agii Anargyri Anticancer Hospital of Athens	E. Xydakis, G. Panagos
1st Department of Pulmonary Diseases, Sotiria General Hospital of Athens	A. Agelidou, E. Papadakis
3rd Department of Pulmonary Diseases, Sotiria General Hospital of Athens	A. Christou
6th Department of Pulmonary Diseases, Sotiria General Hospital of Athens	M. Toubis
7th Department of Pulmonary Diseases, Sotiria General Hospital of Athens	T. Grigoratou, A. Geroyianni, S. Tzannes
8th Department of Pulmonary Diseases, Sotiria General Hospital of Athens	A. Rapti, G. Pavlakou, E. Tsaroucha, O. Anagnostopoulou
University Department of Pulmonary Diseases, Sotiria General Hospital of Athens	M. Veslemes
Medical Oncology Unit, 3rd Department of Internal Medicine of University of Athens, Sotiria General Hospital of Athens	K. Syrigos
1st Department of Pulmonary Diseases, Sismanoglion General Hospital of Athens	P. Ziotopoulos, P. Palamidas, V. Chandrinos
2nd Department of Pulmonary Disease, Sismanoglion General Hospital of Athens	M. Agelidou, X. Tsiafaki, F. Apostolopoulou
Medical Oncology Unit, Department of Internal Medicine, Elpis Hospital of Athens	C. Latoufis, E. Kakouri
2nd Department of Internal Medicine, NIMTS Hospital of Athens	H. Tsiakopoulos
Department of Pulmonary Diseases, Euroclinic, Athens	E. Zachariadis
Medical Oncology Unit, Department of Propedeutic Medicine of University of Athens, Laiko General Hospital of Athens	A. Polyzos
Medical Oncology Unit, 401 Military Hospital of Athens	C. Christofilakis
1st Department of Medical Oncology, Metaxa Anticancer Hospital of Athens	N. Ziras, A. Potamianou, A. Athanasiou
Department of Internal Medicine, Patision General Hospital of Athens	E. Tselepatiotis
Department of Medical Oncology, General Hospital of Larissa	A. Athanasiadis
Department of Pulmonary Diseases, Hospital of Pulmonary Diseases of Patras	J. Lychros
Department of Medical Oncology, Agios Andreas, Hospital of Patras	P. Ginopoulos, A. Christopoulou, M. Sougleri
Department of Pulmonary Diseases, General Hospital of Korfu	K. Chainis
Department of Pulmonary Diseases, General Hospital of Kavala	S. Bousmoukilia
1st Department of Pulmonary Diseases, Papanikolaou General Hospital of Thessaloniki	N. Galanis
2nd Department of Pulmonary Diseases, Papanikolaou Hospital of Thessaloniki	N. Samaras, E. Milonaki
2nd Department of Medical Oncology, Theagenion Anticancer Hospital of Thessaloniki	I. Boukovinas, P. Papakotoulas, P. Markantonakis, J. Stergiou
Oncology Unit, Galinos Hospital of Thessaloniki	A. Baritz

REFERENCES

1. Ginsberg RJ, Vokes EE, Rosenweig K: Non-small cell lung cancer, in DeVita V Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology (ed. 6). Philadelphia, PA, Lippincott-Raven, 2001, pp 925-983

2. Landis SM, Murray T, Bolden S, et al: Cancer Statistics. Cancer J. Clin Cancer Res 48:6-29, 1998

3. Lubin JM: Lung and larynx, in Cancer Rates and Risks (ed. 4). Bethesda, MD, National Institutes of Health, National Cancer Institute, pp 158-161, 1996

4. Souquet PJ, Chauvin F, Boissel JP, et al: Polychemotherapy in non-small cell lung cancer: A meta-analysis. Lancet 342:19-21, 1993

5. Non-Small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomized clinical trials. BMJ 311:899-909, 1995

6. Albain KS, Growley JJ, Le Blanc M, et al: Survival determinants in extensive disease non-small cell lung cancer: The Southwest Oncology Group experience. J Clin Oncol 9:1618-1626, 1991

7. Lilenbaum RC, Green MR: Novel chemotheraputic agents in the treatment of non-small cell lung cancer. J Clin Oncol 11:1391-1402, 1993

8. Zalcberg J, Millward M, Bishop J, et al: Phase II study of docetaxel and cisplatin in advanced non-small cell lung cancer. J Clin Oncol 16:1948-1953, 1998

9. Georgoulias V, Androulakis N, Dimopoulos AM, et al: First-line treatment of advanced non-small cell lung cancer with docetaxel and cisplatin: A multicenter phase II study. Ann Oncol 9:331-334, 1998

10. Le Chevalier T, Monnier A, Douillard JY, et al: Docetaxel (Taxotere) plus cisplatin: An active and well-tolerated combination in patients with advanced non-small cell lung cancer. Eur J Cancer 34:2032-2036, 1998

11. Crino L, Scagliotti G, Marangolo M, et al: Cisplatin-gemcitabine combination in advanced non-small cell lung cancer: A phase II toxicity, response and survival analysis. J Clin Oncol 15:297-303, 1997

12. Gebbia V, Caruso M, Valenza R, et al: Vinorelbine plus cisplatinum for the treatment of stage IIIB and IV non-small cell lung carcinoma. Anticancer Res 14:1247-1250, 1994

13. Le Chevalier T, Brisgand D, Douillard JY, et al: Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small cell lung cancer: Results of a European multicenter trial including 612 patients. J Clin Oncol 12: 360-367, 1994

14. Fossella F, Pereira JR, von Pawel J, et al: Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non–small-cell lung cancer: The TAX 326 Study Group. J Clin Oncol 21:3016-3024, 2003

15. Schiller JM, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 346:92-98, 2002

16. Comella P, Frasci G, Panza N, et al: Randomized trial comparing cisplatin, gemcitabine, and vinorelbine with either cisplatin and

gemcitabine or cisplatin and vinorelbine in advanced non-small cell lung cancer: Interim analysis of a phase III trial of the Southwest Italy Cooperative Oncology Group. J Clin Oncol 18: 1451-1457, 2000

17. Kelly K, Crowley J, Bunn PA Jr., et al: Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small cell lung cancer: A Southwest Oncology Group trial. J Clin Oncol 19:3210-3218, 2001

18. Scagliotti GV, De Marinis F, Rinaldi M, et al: Phase III randomized trial comparing three platinum-based doublets in advanced non-small cell lung cancer. J Clin Oncol 20:4285-4291, 2002

19. Rizvi NA, Spiridonidis CH, Davis TH, et al: Docetaxel and gemcitabine combination in non-small cell lung cancer. Semin Oncol 26:27-31, 1999 (5 suppl 16)

20. Georgoulias V, Kouroussis Ch, Androulakis N, et al: Front-line treatment of advanced non-small cell lung cancer with docetaxel and gemcitabine: A multicenter phase II trial. J Clin Oncol 17:914-920, 1999

21. Georgoulias V, Papadakis E, Alexopoulos A, et al: Platinum-based and non-platinum-based chemotherapy in advanced non-small cell lung cancer: A randomized multicentre trial. Lancet 357:1478-1484, 2001

22. Kosmidis P, Mylonakis N, Nicolaides C, et al: Paclitaxel plus carboplatin versus gemcitabine plus paclitaxel in advanced non-small cell lung cancer: A phase III randomized trial. J Clin Oncol 20:3578-3585, 2002

23. Gridelli C, Gallo C, Shepherd FA, et al: Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small cell lung cancer. J Clin Oncol 21:3025-3034, 2003

24. Miller AB, Hoogstraten B, Staquet M, et al: Reporting results of cancer treatment. Cancer 47:207-214, 1981

25. Hollen PJ, Gralla RJ, Kris MG, et al: Quality of life assessment in individuals with lung cancer: Testing the Lung Cancer Symptome Scale (LCSS). Eur J Cancer 29:51-58, 1993

26. Hollen PJ, Gralla RJ, Kris RG, et al: Quality of life during clinical trials: Conceptual model for the Lung Cancer Symptom Scale (LCSS). Support Care Cancer 2:213-222, 1994

27. Hollen PJ, Gralla RJ: Comparison of instruments for measuring quality of life in patients with lung cancer. Semin Oncol 23:31-40, 1996 (2 suppl 5)

28. Altman GD: Practical Statistics for Medical Research. London: Chapman and Hall, 1991, pp 23-57

29. Collett D: Modeling Survival Data in Medical Research. London: Chapman and Hall, 1994 pp 53-106

30. Armitage P, Berry G: Statistical Methods in Medical Research, 3rd ed, Oxford: Blackwell Scientific, 1994, pp 503-524

31. Alberola V, Camps C, Provencia M, et al: Cisplatin plus gemcitabine versus a cisplatin-based triplet versus nonplatinum sequential doublets in advanced non–small-cell lung cancer: A Spanish lung Cancer Group phase III randomized trial. J Clin Oncol 21:3207-3213, 2003

32. Giaccone G: Early results of a randomized phase III trial of platinum-containing doublets versus a non-platinum doublet in the treatment of advanced non-small cell lung cancer: European Organization for Research and Treatment of Cancer 08975. Semin Oncol 29:47-49, 2002

33. Schiller JH: Platin or no Platin? That is the question. J Clin Oncol 21:3009-3010, 2003