Chemotherapy for Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Multicenter Italian Lung Cancer in the Elderly Study (MILES) Phase III Randomized Trial

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For the MILES Investigators

Background: **Vinorelbine prolongs survival and improves quality of life in elderly patients with advanced non-small-cell lung cancer (NSCLC). Some studies have also suggested that gemcitabine is well tolerated and effective in such patients. We compared the effectiveness and toxicity of the combination of vinorelbine plus gemcitabine with those of each drug given alone in an open-label, randomized phase III trial in elderly patients with advanced NSCLC.** ***Methods:*** **Patients aged 70 years and older, enrolled between December 1997 and November 2000, were randomly assigned to receive intravenous vinorelbine (30 mg/m^2 of body surface area), gemcitabine (1200 mg/m^2), or vinorelbine (25 mg/m^2) plus gemcitabine (1000 mg/m^2). All treatments were delivered on days 1 and 8 every 3 weeks for a maximum of six cycles. The primary endpoint was survival. Survival curves were drawn using the Kaplan–Meier method and analyzed by the Mantel–Haenszel test. Secondary endpoints were quality of life and toxicity.** ***Results:*** **Of 698 patients available for intention-to-treat analysis, 233 were assigned to receive vinorelbine, 233 to gemcitabine, and 232 to vinorelbine plus gemcitabine. Compared with each single drug, the combination treatment did not improve survival. The hazard ratio of death for patients receiving the combination treatment was 1.17 (95% confidence interval [CI] = 0.95 to 1.44) that of patients receiving vinorelbine and 1.06 (95% CI = 0.86 to 1.29) that of patients receiving gemcitabine. Although quality of life was similar across the three treatment arms, the combination treatment was more toxic than the two drugs given singly.** ***Conclusion:*** **The combination of vinorelbine plus gemcitabine is not more effective than single-agent vinorelbine or gemcitabine in the treatment of elderly patients with advanced NSCLC. [J Natl Cancer Inst 2003;95: 362–72]**

Cytotoxic chemotherapy is widely used to palliate advanced non-small-cell lung cancer (NSCLC). Cisplatin-containing regimens provide a slight advantage over supportive care without antineoplastic drugs (a 6-week increase in median overall survival) but can induce severe toxic effects *(1)*. Consequently, this treatment is frequently contraindicated in elderly patients, who are less likely than younger patients to tolerate its potential toxicity *(2)* due to the age-related reduction in the functional reserve of many organs and comorbid conditions *(3,4)*. Of the estimated 1.2 million people with lung cancer worldwide *(5)*, approximately 300 000 have a diagnosis of NSCLC and are aged 70 years or older *(6)*. Many patients in this subgroup are not offered cytotoxic treatment because of concerns about tolerability and the high risk-to-benefit ratio *(7)*.

To examine whether a noncisplatin, moderately toxic chemotherapy could be effective in the treatment of elderly patients with advanced NSCLC, we performed the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) trial *(8)*. In that study, we showed that treatment with vinorelbine, a semisynthetic vinca alkaloid, improved the outcome of patients compared with supportive care without antineoplastic drugs. Patients receiving vinorelbine had longer survival (median = 28 versus 21 weeks) and better scores for some quality-of-life items than patients who did not receive vinorelbine. Overall, toxicity associated with vinorelbine was mild.

Retrospective subgroup analyses of studies with gemcitabine, a cytosine–arabinoside analogue, which acts by upsetting deoxynucleotide pools and interfering with DNA chain elongation *(9)*, have suggested that this drug can also be effective in elderly patients with advanced NSCLC, with mild toxicity *(10,11)*. In these studies, gemcitabine was administered on days 1, 8, and 15 of 4-week cycles at a dose of 1000 mg/m^2. Based on our previous data with vinorelbine, showing that administration of vinorelbine chemotherapy on day 15 is frequently omitted in elderly patients because of toxicity *(12)* and to administer treatment for the same duration in all the arms of the present study, gemcitabine was scheduled on days 1 and 8 every 3 weeks for six cycles, at a dose of 1200 mg/m^2. The planned dose intensity was similar to the standard *(10,11)*. In a phase I–II study in adult patients with advanced NSCLC, we tested various doses of a combination of vinorelbine plus gemcitabine *(13)*. At the lowest doses (vinorelbine at 25 mg/m^2 and gemcitabine at 1000 mg/m^2 administered on days 1 and 8 every 3 weeks for six

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See "Appendix" for the complete list of collaborating authors and institutions.

See "Notes" following "References."

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cycles) the treatment was active, with a 28% response rate; its toxicity was acceptable, with no grade 4 adverse effects. Thus, this dose level was considered safe for testing in elderly patients with advanced NSCLC.

The present study was planned to compare the efficacy and toxicity of vinorelbine plus gemcitabine with those of the two agents individually in elderly patients with advanced NSCLC. We hypothesized that the combination of the two drugs should prolong patients' survival relative to both of the two drugs given individually.

Patients and Methods

Study Design and Entry Criteria

We conducted a phase III, randomized, open-label, multicenter trial. To be eligible, patients had to be aged 70 years or older; to have cytologically or histologically confirmed NSCLC; to have stage IIIb (with pleural effusion or metastatic supraclavicular lymph nodes) or stage IV disease; to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; and to have adequate organ function. We excluded patients with clinically overt brain metastases and those who had received previous chemotherapy. The independent ethical committees of participating institutions (*see* "Appendix") approved the protocol, and patients gave their written informed consent before enrollment. Enrollment was opened December 1, 1997, and was closed November 3, 2000.

Stratification, Randomization, and Therapy

Patients were stratified according to institution, ECOG performance status (0, 1, or 2), and disease stage (IIIb versus IV). Randomization was performed centrally at the Clinical Trials Office, National Cancer Institute (Naples, Italy), using a computerized procedure of minimization. Patients were randomly assigned in a 1 : 1 : 1 proportion to receive intravenous doses of vinorelbine (30 mg/m^2 of body surface area), gemcitabine (1200 mg/m^2 of body surface area), or a combination of vinorelbine (25 mg/m^2 of body surface area) plus gemcitabine (1000 mg/m^2 of body surface area). All treatments were administered on days 1 and 8 every 3 weeks, for a maximum of six cycles. On days 1 and 8 of each cycle, blood was drawn, and chemotherapy was given only if the patient had a minimum neutrophil count of 1.5×10^9/L, a minimum platelet count of 100×10^9/L, a hemoglobin level of 8.0 g/dL or more, and no sign of organ toxicity (excluding alopecia). If one or more requirements could not be met on day 1, chemotherapy was postponed for up to 2 weeks, after which investigators were free to choose the treatment strategy. Dose reductions were not planned as part of protocol. Administration of chemotherapy on day 8 was also postponed if the minimum requirements were not met. Treatment could be interrupted at any time if the disease progressed. Treatment was discontinued if the patient experienced unacceptable toxicity, refused treatment, or withdrew consent. Antiemetic agents and other supportive treatments were provided at the discretion of the treating physician. Palliative radiotherapy could be delivered if needed; however, simultaneous chemotherapy and radiotherapy were discouraged because of the risk of cumulative toxicity. Second-line treatment or prophylactic use of hematopoietic colony-stimulating factors was not planned as part of protocol.

Evaluation of Patients

Before the study, all patients underwent staging procedures, including a clinical examination, a two-view chest x-ray, a computed tomography of the thorax and abdomen, and a bone scan. Bone scan or computed tomography scan of the brain was required only for patients with suspected bone or brain metastases. Before each administration of chemotherapy, patients underwent a clinical examination consisting of a routine biochemistry workup and blood counts. At baseline and after the third and sixth cycles of chemotherapy, patients underwent an electrocardiogram. Geriatric scales, namely those exploring activities of daily living [ADL *(14)* and instrumental ADL (IADL) *(15)*] were used. These scales were filled in by the investigators at baseline and after the third and the sixth cycles. The European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and lung-cancer-specific module (QLQ-LC13) were used to assess quality of life. The EORTC QLQ-C30 questionnaire consists of multi-item functioning scales, and multi- and single-item scales that evaluate general cancer-related symptoms *(16)*. The EORTC QLQ-LC13 module consists of single items that evaluate specific symptoms of lung cancer *(17)*. Both questionnaires are designed to be completed by the patient.

Evaluation of Toxicity and Response

Toxicity was classified according to World Health Organization criteria *(18)* by clinical investigators at each cycle for each patient. For each patient and each type of toxicity, the worst degree of toxicity experienced throughout the treatment was used for the analysis. Objective responses were evaluated by clinical investigators after the third and sixth treatment cycles by repeating the staging procedures. The best response for each patient was used for the analysis. Response evaluation could be anticipated with respect to planned time points for clinically evident or suspected disease progression. When evaluating patients, a complete response was defined as the disappearance of all known sites of disease; a partial response was defined as a decrease of 50% or more in the sum of the products of the largest perpendicular diameters of measurable lesions, no new lesions, and no progression of any lesion; stable disease was defined as a decrease of less than 50% or an increase of less than 25% in the sum of the products of the largest perpendicular diameters of measurable lesions and no new lesions; and progressive disease was defined as an increase of 25% or more in the size of one or more measurable lesions, or a new lesion. Confirmation of response was not mandatory. Patients who died before the restaging procedures were completed were defined as 'progressed' on the date of death. Patients who stopped treatment because of toxicity or refusal before restaging procedures were defined as 'non-evaluated' and were entered as 'nonresponders' in the response rate calculations. The objective response rate was defined as the proportion of complete and partial responses relative to the total number of patients.

Statistical Analysis

The primary endpoint was survival, which was defined as the time from the date of randomization to the date of death or to the date of study closure. For patients who were lost to follow-up at a given time, survival was defined as the time between the date of randomization and the last date on which the patient was known to be alive. The secondary endpoint, progression-free survival, was defined as the time from the date of randomization to disease progression or to death from disease progression or unknown causes. For patients who were lost to follow-up before disease progression, progression-free survival was conservatively defined as the time from the date of randomization to the last date on which the patient was known to be free of disease progression.

We used the procedure devised by Laska and Meisner *(19)* to test whether the vinorelbine-plus-gemcitabine combination (i.e., the experimental treatment combination) was better than each chemotherapy agent alone. Two null hypotheses were simultaneously tested: H_{0V}, in which vinorelbine was assumed to be as effective as the drug combination, and H_{0G}, in which gemcitabine was assumed to be as effective as the drug combination. The alternative hypothesis (H_1) was that the vinorelbine-plus-gemcitabine combination was more effective than its constituents alone. Thus, for statistical analyses, the drug combination was the only experimental arm. According to the procedure adopted, two one-tailed comparisons were planned *a priori:* combination (vinorelbine plus gemcitabine) versus vinorelbine, and combination (vinorelbine plus gemcitabine) versus gemcitabine. The results of both tests had to be statistically significant at the predefined one-tailed alpha level of 0.05 to reject the combined null hypotheses. This procedure is called 'min test' *(19)* and precludes a comparison of single-agent vinorelbine with single-agent gemcitabine—a question that should be considered within an equivalence study design and one that this investigation was not designed to answer.

Our sample size was calculated assuming a median survival with both single agents of 27 weeks. We estimated that 370 events would be needed in each comparison group to detect an improvement in median survival to 36 weeks, which corresponds to a hazard ratio of 0.75, with a one-tailed alpha error of 5% and a power of 0.87 in each test. The overall power for the two comparisons was 0.76. Based on expected accrual rate, a final sample size of 690 patients had to be accrued in 140 weeks. Two interim survival analyses were planned using an alpha spending function *(20)*, which was based on an O'Brien and Fleming *(21)* sequential group design (EaSt, 1993; Cytel Software Corp., Cambridge, MA). Interim analyses were done by the study statistician (C. Gallo), with blinded treatment labels to determine whether the study should be stopped early. Investigators were informed only that accrual remained open. The results of these analyses did not require that the study be discontinued because one-tailed *P*-boundaries of 0.00002 and 0.002, respectively, were not reached in any of the comparisons.

Survival curves were drawn with the Kaplan–Meier product limit method *(22)* and compared with the Mantel–Haenszel test *(23).* According to the study design, one-tailed *P* values were calculated. Hazard ratios of death and of progression with 95% confidence intervals (CIs) were estimated by using the Cox model *(24)*, with treatment, sex, age, institution by number of enrolled patients, stage of disease, histologic type, ECOG performance status (0, 1, or 2), and major comorbidities (cardiovascular, respiratory, digestive/hepatobiliary, and diabetes) as covariates. Proportional hazards assumption was checked graphically by plotting treatment-specific log-cumulative baseline hazards against time *(25).* Another model, with fewer patients because of missing values, was estimated by adding baseline data of geriatric scales ADL and IADL; data from geriatric scales collected after the third and sixth chemotherapy cycles have not been accounted for in this analysis. Both ADL and IADL baseline values were entered into the Cox proportional hazards model as continuous variables. ADL scores ranged from 0 (unable to perform any activity) to 6 (able to perform all activities). The IADL questionnaire was recoded during the analysis to accommodate a frequent within-form missing phenomenon. This scale explores domains that in Italy are applicable only to women (e.g., cooking and washing clothes). Thus, a raw score was calculated by considering only questions that had been answered by the patients, on the grounds that within-form missing values were primarily a result of inapplicability of the question. The raw score was then linearly transformed in a scale ranging from 0 to 100, with 0 representing the lowest level of ability and 100 representing the highest.

All patients were evaluated for survival according to the intention-to-treat rule. For the evaluation of response, patients achieving a complete or partial response were considered 'responders' and all other patients were considered 'nonresponders.' Response rate of patients in the combination arm was compared with that of patients in the single-agent arms in two separate comparisons by 2 × 2 contingency tables, evaluated by the chi-square test, with two-tailed *P* values (S-PLUS 6.0 Professional, release 1; Insightful Corporation, Seattle, WA).

Similarly, two separate comparisons were made for toxicity (graded 0–4) by means of 5 × 2 contingency tables accounting for the ordering of toxicity categories. Exact two-tailed *P* values were calculated by the Wilcoxon rank-sum test (StatXact Turbo 1992; Cytel Software Corp.).

For the quality-of-life analysis, the EORTC core questionnaire (QLQ-C30) and lung-cancer-specific module (QLQ-LC13) multi-item scales were computed by calculating the mean raw scores of single items and transforming them linearly, so that all scales range from 0 to 100. For single items, only linear transformation was performed. Differences between the scores reported after the third chemotherapy cycle and baseline scores were compared by the Wilcoxon rank-sum test.

RESULTS

Patient Characteristics

Of the 759 patients evaluated for the trial, 707 were randomly assigned between December 1997 and November 2000 (Fig. 1). The reasons for ineligibility included wrong stage (n = 19), deteriorated performance status (n = 2), consent refusal (n = 9), previous chemotherapy (n = 3), brain metastases (n = 11), previous malignant disease (n = 6), comorbidity contraindicating chemotherapy (n = 3), uncertain cytologic diagnosis (n = 1), below minimum required baseline neutrophil count (n = 1), and baseline transaminases higher than required (n = 1). Some patients were declared ineligible for the trial for multiple reasons. Eight patients were excluded after randomization because their center withdrew from the study, and one patient was excluded because he withdrew consent. Thus, 698 patients, enrolled by 77 participating centers, were available for the intention-to-treat analyses. Among 233 patients who were assigned to receive vinorelbine, six were found to be ineligible after randomization (three were younger than age 70 years and three had stage IIIB disease without pleural effusion and metastatic supraclavicular lymph nodes), and six eligible patients had treatment violations (two received gemcitabine and four received no chemotherapy). Among 233 patients assigned to receive gemcitabine, four were found to be ineligible (two had had previous chemotherapy and two had stage IIIB disease without pleural effusion and metastatic supraclavicular lymph nodes),

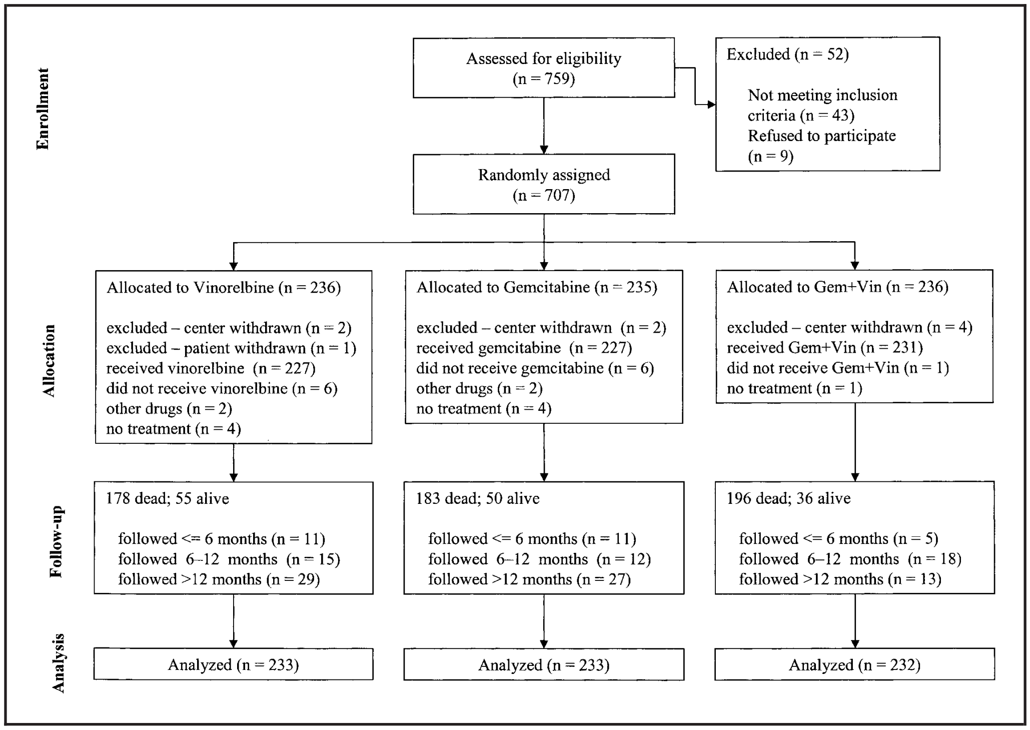


Fig. 1. Flow diagram for the randomized phase III Multicenter Italian Lung Cancer in the Elderly Study trial.

and six eligible patients had treatment violations (one received vinorelbine, one received vinorelbine plus gemcitabine, and four received no chemotherapy). Among 232 patients assigned to receive vinorelbine plus gemcitabine, eight were found to be ineligible (two had had previous chemotherapy, one was younger than age 70 years, and five had stage IIIB disease without pleural effusion and metastatic supraclavicular lymph nodes), and one eligible patient had a treatment violation (no chemotherapy). Treatment violations are summarized in Fig. 1.

The median age of patients was 74 years, range 63–86 (Table 1), and 275 patients (39%) were 75 years old or older. There were slightly fewer females in the vinorelbine arm than in the other two arms. Approximately 70% of the patients had an ECOG performance status of 1 or 2 at baseline. In each arm, more patients had stage IV disease than stage IIIb disease, and more patients had squamous-cell carcinoma than any other histologic type. A median of three organs were affected by cancer. Baseline assessments for ADL and for IADL were missing for 12% of patients. Approximately 14% of patients had some ADL dependency (i.e., an ADL score ≤5), and approximately 60% of patients had some dependency in IADL (score <100%). One-fourth of the patients came from institutions that enrolled 30 or more patients, approximately half the patients came from institutions that enrolled between 10 and 29 patients, and the remainder of the patients came from institutions that enrolled fewer than 10 patients.

Details of comorbidities by treatment arm are reported in Table 2. We found that, when we considered all patients as a group, 11% of the patients had no comorbid disease at entry in the study, and the median number of concomitant non-neoplastic diseases was two. The most frequent comorbidity was cardiovascular (hypertension, arrhythmias, ischemic cardiopathy, previous heart attack or stroke, peripheral or cerebral vasculopathy, or congestive heart failure), which was reported in approximately 60% of patients in each arm. Eighteen patients had aortic aneurisms; four patients had undergone previous cardiovascular surgery for valvular prosthesis, cerebral aneurysmectomy, coronary bypass, or lower limb varices; and one patient had had a pulmonary thromboembolism. Respiratory diseases were reported in more than one-third of the patients, with most of these patients having chronic obstructive pulmonary disease but seven patients having pneumoconiosis and two patients having lung fibrosis. Digestive/hepatobiliary comorbidities (gastritis, peptic ulcer, gallbladder lithiasis, or chronic hepatitis) were reported in less than one-third of all patients, with six patients having undergone major gastrointestinal surgery for peptic ulcers (n = 5) or colostomy for benign disease (n = 1). Genito-urinary comorbidity (benign prostatic hypertrophy, lithiasis, urinary incontinence, or mild chronic renal failure) was reported in more than one-fourth of the patients. Two patients had undergone unilateral nephrectomy. Osteoarticular comorbidities (arthrosis or osteoporosis) were reported in more than 20% of the patients, and two patients had a hip prosthesis. Diabetes was reported in 11% of the patients and was slightly more frequent in patients randomly assigned to the gemcitabine arm (17%) than in those randomly assigned to the other arms (vinorelbine arm, 9%; vinorelbine plus gemcitabine, 8%). Neurologic, psychiatric, hematologic, cutaneous, other endocrinologic, and metabolic comorbidities were each represented in less than 10% of the patients.

Treatment

According to the intention-to-treat principle, all patients, including nine patients who did not receive any chemotherapy and four patients who received the incorrect treatment (Fig. 1), were included in the analysis of treatment administration. Overall, compliance was similar across all three treatments arms. A median number of three cycles was administered within each arm. The median time spent on treatment was 11 weeks for vinorelbine, with 41% of the patients receiving the planned six cycles; 10.3 weeks for gemcitabine, with 39% of the patients receiving all six cycles; and 10 weeks for vinorelbine plus gemcitabine, with 38% of the patients receiving all six cycles. Although dose

Table 1. Baseline characteristics of elderly patients with advanced non–small-cell lung cancer enrolled in the MILES Phase III Randomized Trial*

Characteristic	Vinorelbine (N = 233)	Gemcitabine (N = 233)	Vinorelbine plus gemcitabine (N = 232)
Median age (range), y	74 (63–83)	74 (70–86)	74 (69–84)
Age—no. (%)			
<75	140 (60)	140 (60)	143 (62)
75–79	87 (37)	86 (37)	79 (34)
⩾80	6 (3)	7 (3)	10 (4)
Sex—no. (%)			
Male	204 (88)	193 (83)	184 (79)
Female	29 (12)	40 (17)	48 (21)
ECOG performance status—no. (%)			
0	69 (30)	68 (29)	65 (28)
1	119 (51)	124 (53)	123 (53)
2	45 (19)	41 (18)	44 (19)
Stage—no. (%)			
IIIB	68 (29)	69 (30)	72 (31)
IV	165 (71)	164 (70)	160 (69)
Histologic type—no. (%)			
Squamous	102 (44)	99 (42)	114 (49)
Adenocarcinoma	82 (35)	76 (33)	77 (33)
Large cell	18 (8)	14 (6)	13 (6)
Mixed	3 (1)	8 (3)	4 (2)
Other/not defined	28 (12)	36 (15)	24 (10)
Organs involved by cancer—no. (%)			
1	4 (2)	9 (4)	9 (4)
2	82 (35)	76 (33)	68 (29)
3	87 (37)	88 (38)	92 (40)
4	38 (16)	43 (18)	45 (19)
⩾5	22 (9)	17 (7)	18 (8)
ADL score—no. (%)			
6	165 (71)	180 (77)	170 (73)
5	12 (5)	13 (6)	17 (7)
4	7 (3)	7 (3)	8 (3)
3	7 (3)	2 (<1)	3 (1)
2	3 (1)	1 (<1)	4 (2)
1	2 (<1)	2 (<1)	1 (<1)
0	7 (3)	1 (<1)	2 (<1)
Not available	30 (13)	27 (12)	27 (12)
IADL independency—no. (%)			
100	65 (28)	68 (29)	64 (28)
75–99	52 (22)	51 (22)	55 (24)
50–74	47 (20)	50 (21)	44 (19)
25–49	33 (14)	30 (13)	29 (12)
0–24	6 (3)	7 (3)	12 (5)
Not available	30 (13)	27 (12)	28 (12)
Institution by no. of enrolled patients—no. (%)			
⩾30	56 (24)	57 (24)	60 (26)
10–29	110 (47)	104 (45)	108 (47)
<10	67 (29)	72 (31)	64 (28)

*Because of rounding, percentages may not total 100. ECOG = Eastern Cooperative Oncology Group. ADL score is the number of everyday activities in which the patient is independent; IADL independency is the percentage of everyday instrumental activities in which the patient is independent; MILES = The Multicenter Italian Lung Cancer in the Elderly Study.

Table 2. Baseline comorbidities*

Type	Vinorelbine (N = 233)	Gemcitabine (N = 233)	Vinorelbine plus gemcitabine (N = 232)
Any—no. (%)			
None	23 (10)	25 (11)	30 (13)
1	59 (25)	46 (20)	49 (21)
2	48 (21)	53 (23)	50 (22)
3	43 (18)	42 (18)	53 (23)
4 or more	60 (26)	67 (29)	50 (22)
Cardiovascular—no. (%)	136 (58)	141 (61)	143 (62)
Respiratory—no. (%)	88 (38)	88 (38)	71 (31)
Digestive/hepatobiliary—no. (%)	76 (33)	73 (31)	73 (31)
Genito-urinary—no. (%)	62 (27)	60 (26)	62 (27)
Osteoarticular—no. (%)	47 (20)	56 (24)	45 (19)
Neurologic or psychiatric—no. (%)	11 (5)	16 (7)	14 (6)
Diabetes—no. (%)	20 (9)	39 (17)	19 (8)
Hematologic—no. (%)	3 (1)	1 (<1)	1 (<1)
Cutaneous—no. (%)	10 (4)	9 (4)	7 (3)
Endocrinologic/metabolism—no. (%)	7 (3)	5 (2)	7 (3)

*Because of rounding, percentages may not total 100.

reductions were not planned, they occurred in 6% of administrations after day 1 of the first cycle; the rates of cycles with dose reduction were similar across the three arms. Chemotherapy was omitted on day 8 in 288 (11%) cycles, and the overall rate of omission of day 8 chemotherapy specifically by cycle was similar across the three arms. Treatment was stopped before the sixth cycle because of progressive disease or death in 42%, 46%, and 39% of patients; because of toxicity in 7%, 7%, and 11% of patients; and because of other causes (including patient's choice) in 9%, 8%, and 12% of patients in the vinorelbine, gemcitabine, and vinorelbine plus gemcitabine arms, respectively. Second-line chemotherapy was not planned. However, of patients in the vinorelbine arm, 28 (12%) received second-line treatment, of whom 19 received gemcitabine; of patients in the gemcitabine arm, 30 (13%) received second-line treatment, of whom 20 received vinorelbine; and of patients in the combination arm, 14 (6%) received second-line treatment with other drugs.

Efficacy

Two interim survival analyses, planned *a priori*, were conducted in March and November 1999, with 212 and 408 patients and 98 and 213 deaths, respectively. The results of these analyses did not require that the study be discontinued, because one-tailed *P*-boundaries of 0.00002 and 0.002, respectively, were not reached in any of the comparisons.

By July 20, 2001, 557 (80%) patients had died. Compared with single-agent vinorelbine and single-agent gemcitabine, the combination of vinorelbine plus gemcitabine did not improve survival (Table 3 and Fig. 2). For patients in the vinorelbine arm, median survival was 36 weeks (95% CI = 30 to 45 weeks), with an estimated probability of being alive at 1 year of 0.38. For patients in the gemcitabine arm, median survival was 28 weeks (95% CI = 25 to 34 weeks), with an estimated probability of being alive at 1 year of 0.28. For patients in the combination arm, median survival was 30 weeks (95% CI = 27 to 36 weeks), with an estimated probability of being alive at 1 year of 0.30. Univariate analysis showed no statistically significant difference in survival (combination versus vinorelbine, one-tailed $P = .93$; combination versus gemcitabine, one-tailed $P = .65$). Prespecified multivariable analysis, adjusted for institution by number of enrolled patients, sex, age, ECOG performance status, tumor stage and histologic type, and major comorbidities (cardiovascular, respiratory, digestive/hepatobiliary, and diabetes), showed no statistically significant differences in treatment effects for either statistical comparison. Hazard ratios of death were 1.17 (95% CI = 0.95 to 1.44) for vinorelbine plus gemcitabine ver-

Table 3. Intention-to-treat analysis of efficacy

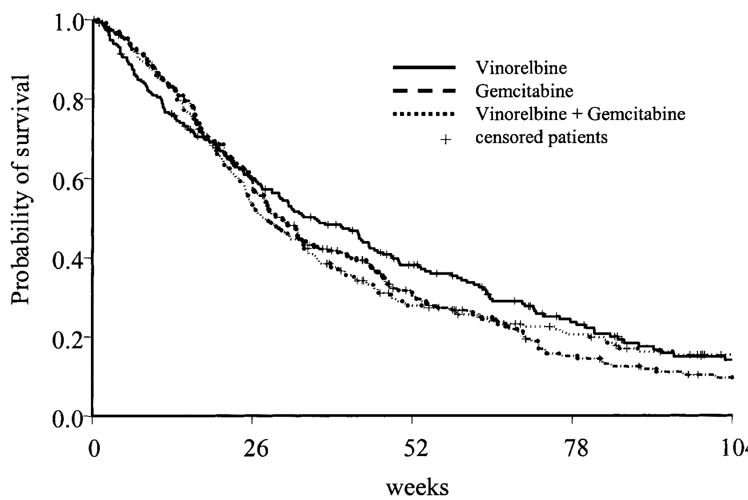
Endpoint	Vinorelbine (N = 233)	Gemcitabine (N = 233)	Vinorelbine plus gemcitabine (N = 232)	Vinorelbine plus gemcitabine vs. vinorelbine		Vinorelbine plus gemcitabine vs. gemcitabine	
				HR (95% CI)*	*P* value	HR (95% CI)*	*P* value
Survival							
No. (%) of events	178 (76)	183 (79)	196 (84)				
Median (95% CI), wk	36 (30 to 45)	28 (25 to 34)	30 (27 to 36)	1.17 (0.95 to 1.44)	0.93**	1.06 (0.86 to 1.29)	0.69**
6-mo probability	0.60	0.53	0.57				
1-y probability	0.38	0.28	0.30				
Time-to-progression							
No. (%) of events	209 (90)	209 (90)	205 (88)				
Median (95% CI), wk	18 (13 to 20)	17 (13 to 19)	19 (16 to 21)	0.95 (0.78 to 1.16)	0.32**	0.95 (0.78 to 1.16)	0.31**
6-mo probability	0.32	0.29	0.34				
1-y probability	0.14	0.13	0.16				
Objective tumor response							
Response rate, %	18	16†	21		0.47§		0.18§
95% CI	13 to 23	12 to 21	16 to 26				

*The Cox model was used, adjusted by volume of the institution; sex, age, and performance status of the patient; stage and histologic type of the tumor; and major comorbidities; HR = hazard ratio; CI = confidence interval.

**One-tailed *P* values are derived from the Cox model.

†Of 232 patients (one patient removed because not eligible for response assessment).

§The chi-square test was used.

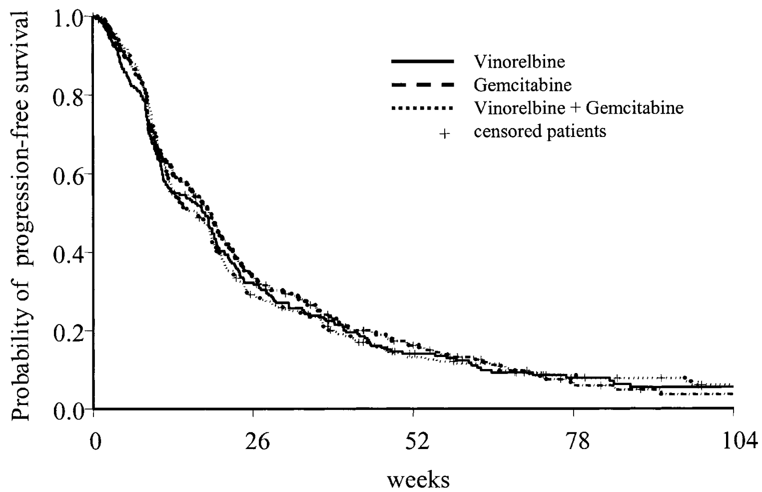


	0	26	52	78	104
Vinorelbine					
Pts at risk	233	132	74	34	16
Point estimate		0.60 (0.54 to 0.67)	0.38 (0.32 to 0.45)	0.24 (0.18 to 0.31)	0.14 (0.09 to 0.21)
Gemcitabine					
Pts at risk	233	118	53	31	20
Point estimate		0.53 (0.47 to 0.60)	0.28 (0.22 to 0.35)	0.21 (0.15 to 0.27)	0.15 (0.11 to 0.22)
Combination					
Pts at risk	232	135	57	25	12
Point estimate		0.57 (0.51 to 0.64)	0.30 (0.24 to 0.37)	0.15 (0.11 to 0.21)	0.09 (0.05 to 0.14)

Fig. 2. Survival curves for elderly patients with advanced non-small-cell lung cancer enrolled in the randomized phase III Multicenter Italian Lung Cancer in the Elderly Study according to treatment arm. **Solid line** = vinorelbine; **dashed line** = gemcitabine; **dotted line** = vinorelbine plus gemcitabine; **vertical dashes** indicate censored patients. The 95% confidence intervals are provided in parentheses for point estimates.

sus vinorelbine and 1.06 (95% CI = 0.86 to 1.29) for vinorelbine plus gemcitabine versus gemcitabine. Of the 698 patients, 611 completed ADL and IADL questionnaires. Exploratory multivariable analysis that included ADL and IADL data in the model resulted in hazard ratios that were similar to those of the model including all the 698 patients, confirming that the combination treatment of vinorelbine plus gemcitabine does not improve survival.

Similar results were obtained in progression-free survival analyses (Fig. 3). At the time of analysis (July 20, 2001), 618 (89%) patients had progressive disease. The median time to progression was 18 weeks (95% CI = 13 to 20 weeks) among patients assigned to receive vinorelbine, 17 weeks (95% CI = 13 to 19 weeks) among patients assigned to receive gemcitabine, and 19 weeks (95% CI = 16 to 21 weeks) among patients assigned to receive the combination of vinorelbine plus gemcitabine. Univariate and multivariable analyses showed no statistically significant differences in either statistical comparison (combination treatment versus vinorelbine and combination treatment versus gemcitabine).



	0	26	52	78	104
Vinorelbine					
Pts at risk	233	74	27	12	8
Point estimate		0.32 (0.27 to 0.39)	0.14 (0.10 to 0.20)	0.08 (0.05 to 0.13)	0.06 (0.03 to 0.10)
Gemcitabine					
Pts at risk	233	64	26	13	8
Point estimate		0.29 (0.24 to 0.36)	0.13 (0.09 to 0.19)	0.08 (0.05 to 0.14)	0.06 (0.03 to 0.11)
Combination					
Pts at risk	232	76	30	8	4
Point estimate		0.34 (0.28 to 0.41)	0.16 (0.12 to 0.22)	0.06 (0.03 to 0.11)	0.04 (0.01 to 0.09)

Fig. 3. Progression-free survival curves for elderly patients with advanced non-small-cell lung cancer enrolled in the randomized phase III Multicenter Italian Lung Cancer in the Elderly Study according to treatment arm. **Solid line** = vinorelbine; **dashed line** = gemcitabine; **dotted line** = vinorelbine plus gemcitabine; **vertical dashes** indicate censored patients. The 95% confidence intervals are provided in parentheses for point estimates.

One patient found to be ineligible after randomization because of wrong staging and rendered disease-free by surgery was removed from the response analysis. A total of 697 patients were analyzed for response. The objective response rate was 18% (95% CI = 13% to 23%) among patients assigned to receive vinorelbine, 16% (95% CI = 12% to 21%) among those assigned to receive gemcitabine, and 21% (95% CI = 16% to 26%) among those assigned to receive the combination of vinorelbine plus gemcitabine. Differences in objective response rates were not statistically significant (vinorelbine plus gemcitabine versus vinorelbine, chi-square $P = .47$; vinorelbine plus gemcitabine versus gemcitabine, chi-square $P = .18$).

Toxicity

The nine patients who did not receive chemotherapy were excluded from the analysis of toxicity, whereas four patients who received incorrect treatment were included, according to the intention-to-treat principle. The combination of vinorelbine plus gemcitabine resulted in more thrombocytopenia and hepatic toxicity than single-agent vinorelbine; the combination treatment also resulted in more neutropenia, vomiting, fatigue, extravasation sequelae, cardiac toxicity, and constipation than single-agent gemcitabine (Table 4).

Quality of Life

Quality-of-life questionnaires were completed at the end of the third chemotherapy cycle by 346 (59%) of the 585 patients who had completed the baseline questionnaires. The rate of missing data was similar among patients in each of the three arms. There were no statistically significant differences in functional and symptom scales between patients assigned to the combination treatment and those patients assigned to single-drug treatments. Hair loss, as estimated by the patients, was statistically significantly worse for those who received the combination of vinorelbine plus gemcitabine than for those who received gemcitabine ($P = .03$). For those who received vinorelbine, there were no statistically significant differences as compared with those who received the combination.

Discussion

This phase III randomized study shows that the combination of vinorelbine plus gemcitabine has no advantage over either single agent in the treatment of elderly patients with advanced NSCLC. Vinorelbine was shown to be effective in the first randomized trial conducted in elderly patients with advanced NSCLC *(8)*. Use of single-agent gemcitabine for the treatment of NSCLC was justified by retrospective studies *(10,11)*, and subsequently corroborated in prospective phase II studies in elderly patients *(26,27)*. Gemcitabine is one of the most widely used drugs in clinical practice against NSCLC because of its low toxicity. Similarly, the combination of vinorelbine plus gemcitabine is frequently used in elderly patients or in those with poor performance status because it is less toxic than cisplatin-based regimens, although its efficacy is unproven. Consequently, the finding that vinorelbine plus gemcitabine is no better than either single agent will be of interest to those involved in clinical practice and will result in savings in terms of costs and toxicity.

A general consideration underlying the design of this study was that elderly patients with advanced NSCLC are usually not eligible for aggressive cisplatin-based chemotherapy because of the age-related reduction of the functional reserve of many organs and comorbidities *(3,4)*. Until some years ago, cisplatin-based chemotherapy was the only choice of treatment for ad-

Table 4. Percentage of patients with toxicity by World Health Organization grade and study arm

Side effect	Vinorelbine (N = 229)				Gemcitabine (N = 228*)				Vinorelbine plus gemcitabine (N = 231)				Combination vs. vinorelbine	Combination vs. gemcitabine
Grade	1	2	3	4	1	2	3	4	1	2	3	4	*P*†	*P*†
Anemia	21	10	3	<1	18	10	2	—	27	13	2	—	.10	.009
Neutropenia	14	9	14	11	12	11	7	1	16	16	13	5	.58	<.0001
Platelets	5	1	<1	—	9	4	2	1	13	4	3	<1	<.0001	.16
Infection	2	3	3	—	2	3	—	—	5	4	—	1	.63	.11
Bleeding	1	—	1	—	1	1	—	—	2	<1	—	—	.99	.99
Nausea/vomiting	24	7	<1	—	19	3	1	—	29	8	1	—	.15	.0005
Diarrhea	3	1	—	—	1	—	<1	—	3	1	1	—	.51	.05
Mucositis	7	1	1	—	6	2	<1	—	8	3	<1	—	.71	.48
Fatigue	24	16	7	—	21	14	6	—	19	22	6	1	.45	.04
Allergy	—	—	—	—	<1	<1	—	—	1	1	—	—	.06	.40
Skin	<1	<1	—	—	1	<1	—	—	3	<1	<1	—	.09	.33
Extravasation	2	1	1	—	<1	—	—	—	5	1	<1	—	.39	.0007
Fever	9	6	2	—	14	5	1	—	10	10	<1	1	.26	.52
Cardiac	<1	1	1	<1	—	<1	—	1	1	2	3	<1	.16	.03
Pulmonary	2	3	1	—	1	3	<1	<1	2	2	1	<1	.80	.89
Renal	2	1	—	—	3	—	—	—	2	—	—	—	.41	.38
Hepatic	2	<1	<1	—	7	2	—	<1	6	3	1	—	.002	.84
Constipation	19	12	3	<1	14	4	—	—	23	11	2	—	.99	<.0001
Peripheral neurotoxicity	8	1	1	—	3	1	—	—	6	1	—	—	.16	.13
Central neurotoxicity	<1	<1	—	<1	—	<1	—	—	1	1	—	—	.71	.22

*Toxicity data were not available for one patient.

†Exact *P* values were obtained from ordered 5×2 contingency tables by Wilcoxon rank-sum test. — = No patients showed toxicity of that grade.

vanced NSCLC, based on results of trials performed during the 1980s and the early 1990s *(1)*. Consequently, during those years, only one-fourth of patients in the United States who were over the age of 65 with metastatic lung cancer received chemotherapy *(28)*. The low rate of treated patients could be only partially attributed to referral patterns because age, comorbidity, sex, and race/ethnicity were independent determinants of treatment when an oncologist took care of the patients *(28)*. Thus, cisplatin-based chemotherapy is probably not a useful tool for the treatment of elderly NSCLC patients. By contrast, Langer et al. *(29)* recently suggested that cisplatin-based therapy should not be denied to well-performing elderly patients with advanced NSCLC. This suggestion was made on the basis of a retrospective analysis of the ECOG 5592 trial of three cisplatin-based regimens, which showed that main treatment outcomes did not differ between the adult patients and the elderly patients (84 septuagenarians and two octogenarians), who represented 15% of the study population *(29)*. Because approximately 30% of those diagnosed with NSCLC are elderly patients *(2)*, underrepresentation of elderly patients in clinical studies of NSCLC may be associated with a selection of those patients who have a better prognosis and can better tolerate treatment. Thus, generalizability of results to the whole population of elderly people remains questionable *(30)*. Currently, there are no reliable and prospective data on the safety of cisplatin-based chemotherapy in elderly patients.

For our study, the minimum required age of 70 years ensured that the enrolled patients would be more representative of elderly patients with advanced NSCLC than those patients recruited in clinical trials with no upper age limit, i.e., studies that enroll both adults and elderly patients. Indeed, studies of the latter type *(31,32)* usually have eligibility criteria designed for adult patients, and eligible elderly patients may represent a selected subgroup, presumably with a better prognosis and higher treatment compliance than the whole elderly population. Thus, information from such selected patients, particularly for clinical trials with aggressive and potentially toxic treatment approaches [e.g., cisplatin-based chemotherapy *(29)*], can be misleading and unsafe when generalized to clinical practice. Designing clinical trials with a minimum patient age of 70 years and no upper limit is an appropriate method to reduce selection bias and improve the generalizability of data on the treatment of elderly cancer patients.

In this study, geriatric scales measuring the ability to perform everyday activities were evaluated to determine whether they provide information useful for tailoring chemotherapy to elderly patients. The addition of baseline values of the geriatric scales to the multivariable analysis did not affect the primary study results, which indicated that the degree of ADL and IADL dependency does not affect treatments under investigation in the MILES study. Nevertheless, because such scales could have some prognostic validity, we are planning a more in-depth analysis of their prognostic value, which will be reported elsewhere.

Our findings contrast with those of Frasci et al. *(33)*, who carried out a small randomized study of 120 elderly patients with advanced NSCLC that was stopped after an interim analysis showed better patient survival with vinorelbine plus gemcitabine than with vinorelbine alone. In that study, the data were impressive because of the unfavorable prognosis of patients in the vinorelbine (control) arm (18 weeks median survival) that produced a surprisingly low hazard ratio of death (0.48). This negative outcome associated with vinorelbine treatment is not consistent with other trials testing this drug in elderly and adult patients *(8,34–36)*; however, it is similar to the outcome frequently associated with supportive care alone *(8,37)*. Frasci et al. *(33)* used approximately 20% higher doses of both drugs in the combination (30 mg/m^2 vinorelbine and 1200 mg/m^2 gemcitabine, on days 1 and 8 every 21 days) than were used in our trial. In a phase I trial, we found that such high doses were not well tolerated in adult patients *(13)*. Moreover, we found no dose-effect in three doses of the tested vinorelbine-plus-gemcitabine combination in a randomized phase II study *(13)*. Therefore, biases in patient selection rather than higher doses may explain the results of Frasci et al. *(33)*.

There are at least three possible ways to explain why the combination of vinorelbine plus gemcitabine was not better than either single agent. One possibility is that polychemotherapy was not better than single-agent treatment because of toxicity and lack of compliance. However, although combined treatment was more toxic than single-agent treatment, its toxicity was acceptable, and the slightly lower compliance in patients treated with the combination cannot account for the lack of efficacy. A second possibility is that our survival results could have been blunted by second-line treatment and eventual crossover in the single-drug arms. Such effects would mimic sequential treatment with the same drugs given in the combination arm. However, few patients (10.3%) received second-line chemotherapy, and the time to progression, which is not affected by this potential bias, was similar in all three arms. A third possibility is that the combination of vinorelbine plus gemcitabine, although acting through different mechanisms, exerted antagonistic, nonsynergistic, or nonadditive effects on the patient outcomes. Antagonistic or at least nonsynergistic effects of the combination of vinorelbine plus gemcitabine have been shown in a breast cancer estrogen-dependent cell line *(38)*. However, laboratory evidence of these effects is weak, and there are conflicting data showing additive activity over a wide range of doses tested in the mouse Lewis lung carcinoma model *(39)*.

Because the results of the MILES trial do not rule out the possibility that other regimens of polychemotherapy could be more effective than single-agent chemotherapy in the treatment of elderly patients with advanced NSCLC, feasibility of different combinations should be explored. Based on considerations and data available to date *(1,29,34,40)*, cisplatin-based combinations, which are commonly used in the treatment of adult patients with advanced NSCLC, should be prospectively studied, and investigators should look for schedules and doses that can improve compliance in elderly patients. Similarly, carboplatin-containing combinations should be prospectively tested in clinical trials dedicated to elderly patients, on the basis of recent evidence regarding the efficacy of carboplatin and paclitaxel and the suggestion that the effect of carboplatin is similar in groups of adult and elderly patients *(41)*.

While waiting for these new studies to be done, we recommend that single-agent chemotherapy (vinorelbine or gemcitabine) should be preferred over the combination treatment as palliative treatment for elderly patients with advanced NSCLC. Design of the MILES study does not allow formal comparison of the arms with single-agent chemotherapy. Clinical sense, toxicity profile of each drug, patient comorbidities, cost considerations, and patient preferences should drive the choice of vinorelbine or gemcitabine, which should both be considered as valuable therapeutic options.

Appendix

The following is a list of participating institutions and coauthors (* denotes institutions that participate in the activities of the Gruppo Oncologico Italia Meridionale [GOIM] group):

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Notes

Editor's note: C. Gridelli conducts research sponsored by AstraZeneca, serves on an advisory board for AstraZeneca, and is a member of the speaker's bureaus for Eli Lilly, Pierre Fabre, AstraZeneca, Roche, Glaxo Smith-Kline, Bristol-Myers Squibb, and Aventis. F. Perrone serves on an advisory board for AstraZeneca. F. Perrone and C. Gallo have obtained honoraria from Glaxo Smith-Kline for editorial activities. A. Rossi has conducted research sponsored by AstraZeneca and is a member of the speaker's bureau for Pierre Fabre. L. Frontini is a member of the speaker's bureaus for Pierre Fabre and Eli Lilly. S. Cigolari has received a grant from Pierre Fabre for a scientific symposium.

C. Gridelli was the principal investigator, F. Perrone headed the coordinating office, and C. Gallo was the head biostatistician. C. Gridelli, F. Perrone, and C. Gallo drafted the final manuscript. All investigators participated in a steering committee that discussed the protocol, periodically reviewed blinded progress reports, reviewed the draft of the manuscript, and contributed to its final version. All but F. Perrone and C. Gallo enrolled patients into the study. The other MILES investigators who enrolled patients or collaborated with those listed in the title are listed in the Appendix.

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