Randomized Study of Maintenance Vinorelbine in Responders With Advanced Non–Small-Cell Lung Cancer

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Background: **Prolongation of chemotherapy duration, usually referred to as maintenance chemotherapy, has been considered as an approach to improve survival of patients with advanced non–small-cell lung cancer (NSCLC). If the maintenance regimen differs from the induction regimen, patients will receive not only higher total doses of chemotherapy but also earlier delivery of non–cross-resistant agents. We conducted a randomized trial to compare maintenance vinorelbine therapy with observation in previously untreated patients who responded to induction treatment with mitomycin–ifosfamide–cisplatin (MIC).** ***Methods:*** **Patients with stage IIIB NSCLC were treated with two monthly MIC cycles followed by radiotherapy; those with "wet" stage IIIB (pleural or pericardial involvement), with stage IIIB with supraclavicular node involvement, or stage IV (i.e., metastatic) NSCLC were treated with four monthly MIC cycles. Patients who responded to induction treatment were randomly assigned to receive intravenous vinorelbine at a dose of 25 $mg \cdot m^{-2} \cdot wk^{-1}$ for 6 months or no further treatment. Survival comparisons used the log-rank test and the Cox regression adjusted for stage. All statistical tests were two-sided.** ***Results:*** **A total of 573 patients were registered, of whom 227 responded to induction treatment and 181 were randomly assigned (91 to maintenance vinorelbine and 90 to observation) between January 1994 and March 2000. One- and 2-year survival rates were 42.2% and 20.1% in the vinorelbine arm and 50.6% and 20.2% in the observation arm, respectively (log-rank $P = .48$). The hazard ratio of survival after adjustment on stage, in the vinorelbine arm relative to the observation arm, was 1.08 (95% confidence interval = 0.79 to 1.47; $P = .65$). There was also no difference between arms in progression-free survival (log-rank $P = .32$).** ***Conclusion:*** **Maintenance vinorelbine did not improve survival of patients with advanced NSCLC who responded to induction MIC treatment. Nevertheless, other agents, including docetaxel and targeted agents, should be evaluated as maintenance agents before the concept is abandoned. [J Natl Cancer Inst 2005;97:499–506]**

Non–small-cell lung cancer (NSCLC) remains a leading cause of cancer-related mortality in developed countries, because of both high incidence and the lack of curative treatment for advanced disease. With 1-year survival rates of 30%–40% and 2-year survival rates of less than 15% with standard cisplatin-based chemotherapy, many attempts are being made to prolong survival of patients with stage IIIB and IV (i.e., metastatic) NSCLC. Although new agents, both chemotherapeutic and targeted molecules, are being developed, efforts to optimize delivery of existing chemotherapy agents are ongoing.

One approach to optimizing chemotherapy consists of increasing its intensity, which can be achieved by delivering higher dose intensities or higher total doses of chemotherapy. Maintenance chemotherapy, which involves prolongation of chemotherapy duration, either with the same regimen as that used for induction treatment or with other agents, increases total doses of chemotherapy. Delivering different chemotherapy regimens for induction and maintenance also has a theoretical advantage. According to the Goldie and Coldman hypothesis of drug resistance *(1)*, the appearance of resistant cells depends on spontaneous mutations and increases with time. Therefore, the early use of non–cross-resistant antineoplastic agents might increase the probability of destroying more cancer cells before chemoresistance arises *(1)*. On this basis, benefit could be expected from maintenance delivery of one or several drugs different from those given as induction treatment.

Presumably, patients who respond to front-line chemotherapy can be considered as having chemosensitive disease and are the most likely to derive clinical benefit from maintenance chemotherapy. Indeed, among 13 published randomized phase III trials of maintenance chemotherapy in small-cell lung cancer *(2)*, the only trial to have shown a statistically significant survival advantage of maintenance chemotherapy was carried out only in patients who responded to induction chemotherapy *(3)*. Therefore, we conducted a randomized trial among patients who responded to induction chemotherapy or chemoradiation

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See "Notes" following "References."

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with mitomycin–ifosfamide–cisplatin (MIC) to compare survival of such patients treated with maintenance single-agent vinorelbine with that of patients not receiving maintenance chemotherapy.

Subjects and Methods

Patient Eligibility

Patients with histologically confirmed stage IIIB and IV NSCLC were eligible for this study *(4)*. Patients came from Armentières, Brive-la-Gaillarde, Belfort, Bourges, Beauvais, Le Mans, Montluçon, Meaux, Nevers, Saintes, Saint Brieuc, Sens, Saint Omer, Troyes, Vesoul, and Verdun General Hospitals; Besançon, Grenoble, Nancy, Strasbourg (Hautepierre and Hôpital civil), Tenon (Paris), and Tours University Hospitals; and Dijon Cancer Center, France. Patients were required to have received no prior chemotherapy or thoracic radiotherapy, but patients who experienced recurrences after surgery were eligible. Additional eligibility criteria included a performance status of 2 or less according to World Health Organization (WHO) criteria *(5)*, age 75 years or less, no brain metastases, no previous cancer except for basal cell carcinoma of the skin, no interstitial pneumonitis, no severe cardiac disease, and no cirrhosis. Patients with stage IIIB disease were required to have no contraindications to thoracic radiotherapy. Biologic requirements included a leukocyte count above 3000/μL, a neutrophil count above 1500/μL, a platelet count above 150 000/μL, and a serum creatinine level below 130 μmol/L. Signed informed consent was obtained from all patients registered in the trial, and the study was approved by the Besançon University Hospital Medical Ethics Committee.

All eligible patients were evaluated before registration by physical examination; chest x-ray; computed tomography (CT) scans of the chest, upper abdomen, and brain; abdominal ultrasonography; fiberoptic bronchoscopy with biopsies; complete blood cell count; and creatinine determination.

Treatment

The treatment plan is illustrated in Fig. 1. All patients registered in the study received intravenous MIC (mitomycin C at 6 $mg \cdot m^{-2}$ on day 1, ifosfamide at 1.5 $g \cdot m^{-2} \cdot day^{-1}$ on days 1 through 3, and cisplatin at 30 $mg \cdot m^{-2} \cdot day^{-1}$ on days 1 through 3). Cisplatin was administered first, as a 45-minute infusion in a 5% NaCl solution with standard hydration. Prophylaxis of the bladder toxicity of ifosfamide consisted of 1.2 $g \cdot m^{-2} \cdot day^{-1}$ of mesna. Modalities of antiemetic therapy were let to the discretion of investigators according to the participating centers' policies. MIC cycles were repeated every 4 weeks for a total of two cycles for patients with stage IIIB disease and a total of four cycles for patients with "wet" stage IIIB (i.e., pleural or pericardial involvement), stage IIIB with supraclavicular node involvement, or stage IV NSCLC. At each cycle, patients had a blood cell count on days 10 and 28 and a creatinine determination on day 28. If granulocyte counts were between 1000 and 1500/μL on day 28, the doses of mitomycin and ifosfamide were reduced by 50%. If granulocyte counts were less than 1000/μL, the next treatment cycle was delayed for 1 week. If platelet counts were between 100 000/μL and 150 000/μL, the dose of mitomycin was reduced by 50%, and if platelet counts were below 100 000, mitomycin was omitted entirely. If the creatinine level was between 130 and 180 μmol/L, cisplatin was reduced by 50%, and if the creatinine level was over 180 μmol/L, MIC chemotherapy was stopped.

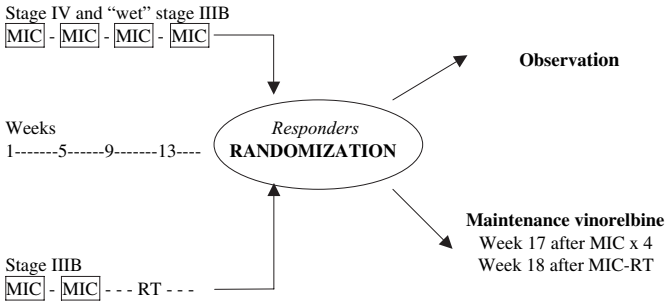

Fig. 1. Induction treatments by stage of the disease and randomization groups. Stage IIIB patients who had pleural and/or pericardial involvement (i.e., "wet" stage IIIB) and/or involvement of the supraclavicular nodes and stage IV patients received four cycles of induction mitomycin C–ifosfamide–cisplatin (MIC) chemotherapy. Stage IIIB patients received two cycles of induction MIC chemotherapy followed by radiation therapy (RT; a total radiation dose of 55–60 Gy in 30 fractions over 6 weeks, including 40 Gy delivered to the whole target volume plus the superior and medium mediastinum and a 15–20 Gy boost administered to the T4 and/or N3 areas). Responding patients were randomly assigned to receive no maintenance chemotherapy or maintenance chemotherapy with vinorelbine (which was administered intravenously at a dose of 25 mg/m^2/wk for 6 months or until progression or any grade 4 toxicity different from neutropenia).

In patients with stage IIIB NSCLC, thoracic radiotherapy began 4 weeks after the second MIC cycle. A total radiation dose of 55–60 Gy in 30 fractions was given over 6 weeks *(6)*, including 40 Gy delivered to the whole target volume plus the superior and medium mediastinum and a 15–20 Gy boost administered to the T4 and/or N3 areas.

Tumor size was evaluated before each chemotherapy cycle using chest x-ray and at completion of the induction treatment (i.e., with MIC or MIC plus radiotherapy) with thoracic and abdominal CT scans, abdominal ultrasonography, and fiberoptic bronchoscopy if the baseline result was abnormal. Tumor response was evaluated according to WHO criteria *(5)*. Patients whose disease showed a complete or a partial response to induction treatment were randomly assigned to receive maintenance vinorelbine or to the observation arm (no maintenance therapy). A complete response was defined as the disappearance of all clinical and radiologic evidence of disease. A partial response was defined as a 50% decrease in the sum of products of the largest perpendicular diameters of the tumors with no evidence of progression in any site. Patients with progressive or stable disease were treated off study at the discretion of investigators.

Patients in the vinorelbine arm were administered vinorelbine intravenously at a dose of 25 $mg \cdot m^{-2} \cdot wk^{-1}$ for 6 months, beginning 16 weeks after the first MIC cycle in patients treated with induction chemotherapy and 17 weeks after the first MIC cycle in patients treated with induction chemoradiation. A blood cell count was performed before every vinorelbine perfusion; the vinorelbine dose was reduced by 50% if granulocyte counts were between 1000 and 1500/μL, and vinorelbine was withheld if granulocyte counts were less than 1000/μL. If granulocyte counts were less than 1000/μL for more than 3 weeks, vinorelbine was restarted on an every-other-week cycle. Prevention of leukoneutropenia using granulocyte colony-stimulating factors

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was not allowed. Maintenance vinorelbine was stopped after any grade 4 toxicity other than neutropenia was observed. In both the vinorelbine and observation groups, tumor response was evaluated by chest x-ray, which was performed monthly during the 6 months after random assignment and every 3 months thereafter. The disease was assessed by planned thoracic CT scan, abdominal ultrasonography, and fiberoptic bronchoscopy at 3, 6, 10, 14, and 18 months after randomization and by thoracic CT scan and fiberoptic bronchoscopy if initially abnormal every 6 months thereafter in the absence of progression.

Investigators were advised to treat patients with progressive disease in both arms with etoposide (80 $mg \cdot m^{-2} \cdot day^{-1}$) and cisplatin (30 $mg \cdot m^{-2} \cdot day^{-1}$) on days 1 through 3 every 4 weeks. Vinorelbine treatment was not allowed in patients assigned to the observation group at any time.

Statistical Analysis

The objective of this phase III study was to compare survival between patients treated with maintenance vinorelbine and patients receiving no further treatment after response to induction treatment. The primary endpoint was overall survival from the date of randomization. The secondary endpoints were progression-free survival; the rate of partial responses that became complete responses according to WHO criteria; the rate of improved partial responses that did not achieve complete response, i.e., a substantial reduction in tumor size in a patient in whom lesion(s) persisted; and the toxicity of maintenance vinorelbine.

Patients were stratified by stage before randomization. Patients were randomized by a phone call to the randomization center during the 18th week after the first MIC cycle for those treated with induction chemoradiation and during the 17th week for those treated with induction chemotherapy. The method of randomization was by random permuted blocks within strata. The block size was six.

The study was designed to have 90% power to test the hypothesis that the 18-month survival rate would be 10% in the observation arm and 20% in the maintenance vinorelbine arm. Assuming an accrual period of 3 years, a potential follow-up of 2 years for the last included patient, and a one-sided test with a type I error rate of 0.05, 270 MIC-responding patients had to be randomly assigned. With an estimated MIC response rate of 40%, 675 patients had to be registered *(7)*. Because accrual took twice as long as initially planned, the study was stopped on January 31, 2000, after 573 patients had been registered. For survival analyses, an end date of January 1, 2002, was chosen because 178 (98%) of the 181 randomized patients had reached the planned potential minimal follow-up from the date of randomization of 2 years. The actual statistical power was calculated using the reduced sample size, the initially hypothesized survival difference, the planned (and actual) follow-up of 2 years, and both the expected and actual duration of inclusion. Whether calculation was based on the expected or the actual duration of inclusion, the 181 randomized patients conferred to the survival comparison a statistical power of approximately 80% and a statistical significance level of .05.

Survival was calculated from the date of randomization for the comparison between both arms. Progression-free survival was the time elapsed between the date of randomization and the date of progression or death. For patients alive and/or progression-free whose last status date was earlier than January 1, 2002, the actual date of last contact was used as the end date. Survival curves were generated using the Kaplan–Meier method *(8)* and were compared with the log-rank test and with Cox proportional hazards regression adjusted for stage *(9)*. The graphical representation of $\log\{-\log [S(t)]\}$ was used to confirm the assumption of proportionality. Differences in toxicities were compared using the Mantel–Haenszel test. All statistical comparisons were two-sided. All calculations were performed on an intention-to-treat basis using SAS software (version 8.2, 1999, SAS Institute Inc., Cary, NC).

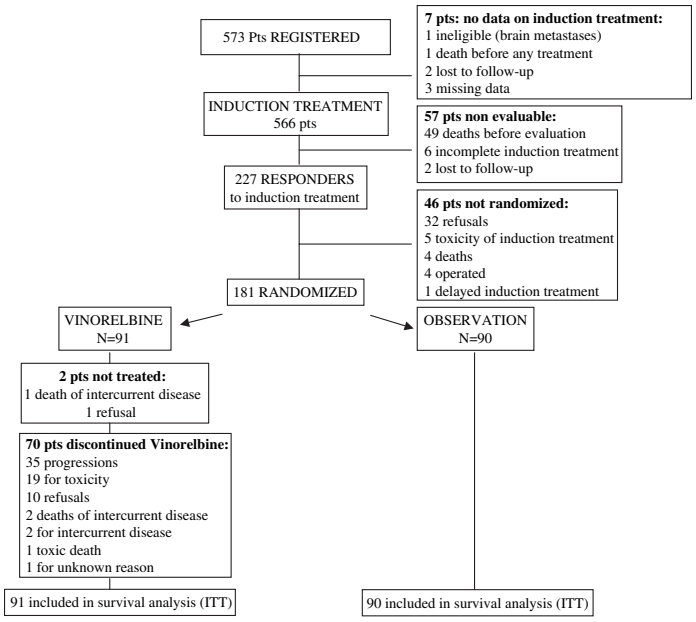

Fig. 2. Flow diagram of the trial. The number of weekly vinorelbine infusions received was as follows: none in two patients, one to three in 11 patients, four to eight in 22 patients, eight to 16 in 30 patients, 16 to 24 in 21 patients, and 25 to 31 in three patients. ITT = intention-to-treat; pts = patients.

Results

Patient Characteristics and Induction Treatment

A total of 573 patients were included in this study between July 1, 1993, and January 31, 2000 (Fig. 2). There were 239 stage IIIB patients and 334 stage IV patients. Baseline patient characteristics are detailed in Table 1. Among stage IIIB patients, two were lost to follow-up, and data on treatment were missing for another two patients. Among stage IV patients, one died before receiving any treatment, one patient was ineligible because of brain metastases, and information on treatment was missing for another patient. Further results are presented for the 566 patients (235 stage IIIB and 331 stage IV) for whom data were available (Fig. 2).

Among the 235 patients treated for a stage IIIB NSCLC, 205 were planned to receive induction chemoradiation. The other 30 had pleural and/or pericardial involvement and/or involvement of the supraclavicular nodes and were therefore planned to receive induction chemotherapy (i.e., four cycles of the MIC regimen). Of the 205 patients who were intended to receive thoracic radiotherapy, only 172 were known to have been irradiated. The other 33 patients received only chemotherapy

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Table 1. Baseline characteristics of patients with advanced non–small-cell lung cancer in the trial*

Patient characteristics	Registered, *N* (%)	Vinorelbine arm, *N* (%)	Observation arm, *N* (%)
Total	573 (100)	91 (100)	90 (100)
Median age, year (range)	60 (30–75)	62 (39–74)	63 (30–75)
Sex			
Male	528 (92.1)	87 (95.6)	81 (90)
Female	45 (7.9)	4 (4.4)	9 (10)
Performance status			
0	174 (30.4)	30 (33)	30 (33.3)
1	316 (55.1)	47 (61.6)	52 (57.8)
2	83 (14.5)	14 (15.4)	8 (8.9)
Histology			
Squamous	277 (48.3)	55 (60.4)	53 (58.9)
Adenocarcinoma	220 (38.4)	28 (30.8)	26 (28.9)
Large cell	76 (13.3)	8 (8.8)	11 (12.2)
Stage			
IIIB†	239 (41.7)	43 (47.3)	51 (56.7)
IV	334 (58.3)	48 (52.7)	39 (43.3)
Response to induction treatment at random assignment‡			
Complete		12 (13.2)	6 (6.7)
Partial		79 (86.8)	84 (93.3)

*MIC = mitomycin–ifosfamide–cisplatin.

†Thirty stage IIIb patients had a pleural and/or pericardial involvement and/or involvement of the supraclavicular nodes.

‡Response to induction therapy according to World Health Organization criteria *(5)*.

Table 2. Response to induction treatment (chemotherapy or chemoradiation) among patients with advanced non–small-cell lung cancer*

Response	Stage IIIB†, *N* (%)	Stage IV, *N* (%)
Total	235 (100)	331 (100)
Complete	17 (7.2)	5 (1.5)
Partial	105 (44.7)	100 (30.2)
Stabilization	18 (7.7)	55 (16.6)
Progression	74 (31.5)	135 (40.8)
Not evaluable	21 (8.9)	36 (10.9)

*Response was determined at completion of the induction therapy (i.e., with mitomycin–ifosfamide–cisplatin [MIC] or MIC plus radiotherapy) with thoracic and abdominal computed tomography scans, abdominal ultrasonography, and fiberoptic bronchoscopy if the baseline fiberoptic result was abnormal. Tumor response was evaluated according to World Health Organization criteria *(5)*. A complete response was defined as the disappearance of all clinical and radiologic evidence of disease. A partial response was defined as a 50% decrease in the sum of products of the largest perpendicular diameters of all tumors with no evidence of progression at any site.

†Among these 235 stage IIIB patients, 172 were treated with chemoradiation and 33 received only chemotherapy.

(one or two MIC cycles) for the following reasons—the patient died before radiotherapy (15 patients), the disease progressed before radiotherapy (14 patients), the patient received surgery (one patient), and the patient refused (one patient)—or were lost to follow-up (two patients).

Seventeen deaths (3%) potentially related to induction treatment occurred among the 566 patients. These 17 deaths include 14 deaths after chemotherapy (10 were septic deaths; two were due to severe physical alteration, i.e., performance status 3 or 4; and two were of unknown cause) and three deaths after chemoradiation (one septic death, one death from pulmonary toxicity, and one death of unknown cause). Grade 3 and 4 hematologic toxicities of the MIC combination consisted of leukopenia in 191 of the 566 patients (33.7%), anemia in 99 of the 566 patients (17.5%), and thrombocytopenia in 121 of the 566 patients (21.4%). Severe peripheral neuropathy was rare (two patients). Grade 3 and 4 pulmonary toxicity considered as potentially due to chemotherapy occurred in nine of the 566 patients (1.6%), and grade 3 and 4 pulmonary toxicity caused by radiotherapy was seen in 10 of the 172 irradiated patients (5.8%).

Of the 566 patients for whom induction treatment data were available, 57 were not evaluable for response (49 patients died before evaluation, treatments for three patients were interrupted for toxicity, one patient refused to continue treatment, one patient with stage IIIB disease was not irradiated, one patient did not receive treatment for unknown reason, and two patients were lost to follow-up). A total of 227 patients responded to induction treatment, with 22 of the 566 patients showing complete responses (3.9%) and 205 showing partial responses (36.2%). These 227 responding patients included 122 stage IIIB patients (response rate = 52%; 95% confidence interval [CI] = 37% to 67%) and 105 stage IV patients (response rate = 32%; 95% CI = 23% to 40%) (Table 2). Among the 566 patients for whom data were available, median overall survival from the date of the first chemotherapy cycle was 9 months, and 1- and 2-year survival rates were 37% and 14%, respectively.

Of the 227 patients who responded to induction treatment, 181 (78%) were randomly assigned to the vinorelbine (91 patients) or observation (90 patients) groups between January 1994 and March 2000. The other 46 responding patients were not included in the randomization for the following reasons: 32 refused, four underwent surgery, one finished induction treatment too late, five experienced toxic effects of induction treatment (infection in three patients, pulmonary toxicity in one patient, and severe deterioration of general status in one patient), three patients died due to effects related to induction treatment, and one died of an unknown cause. Comparison of patient characteristics between the 46 non–randomly assigned responders and the 181 randomly assigned patients showed no differences in age, sex, performance status, histology, stage, and rates of complete and partial responses to induction treatment (data not shown). Of patients with stage IIIB disease, 94 of the 122 responders (77%) were randomly assigned; of patients with stage IV disease, 87 of the 105 responders (83%) were randomly assigned. Both groups were well balanced with respect to age, sex, performance status, histology, stage, and response to induction treatment (Table 1).

Maintenance Chemotherapy Delivery

Complete data on chemotherapy delivery were available for 89 of the 91 patients in the vinorelbine group. The number of weekly vinorelbine infusions received was as follows: none in two patients (one patient refused and one died of intercurrent cause, i.e., disease other than cancer or toxicity of chemotherapy), one to three in 11 patients, four to eight in 22 patients, eight to 16 in 30 patients, 16 to 24 in 21 patients, and 25 to 31 in three patients. The mean duration of vinorelbine chemotherapy was 13.8 weeks (standard deviation = 8.7), the median total delivered dose was 450 mg (range = 0–1565), and the median dose intensity was 23 $mg \cdot m^{-2} \cdot wk^{-1}$ (range = 0–30). Vinorelbine was stopped at the end of the treatment program (i.e., 6 months) in 21 patients (23%) and was stopped early in the other 70 (77%)

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patients as follows: for progressive disease in 35 patients (38%), for toxicity in 19 patients (21%), because of treatment refusal in 10 patients (11%), for death of intercurrent disease in two patients (2%), for development of intercurrent disease in two patients (2%), for toxic death in one patient (who had received induction chemoradiation for stage IIIB disease), and for unknown reasons in one patient.

Toxicity of Maintenance Chemotherapy

Two of the 91 patients in the vinorelbine group did not receive vinorelbine (one patient refused and one died of intercurrent cause), and data on toxicity of maintenance vinorelbine were not available for two patients. Toxicities of maintenance vinorelbine for the remaining 87 patients are presented in Table 3. The main toxicity was hematologic. Grade 3 and 4 leukopenia and infections were more frequently observed in patients who had received induction chemoradiation than in those who received induction chemotherapy ($P = .05$ and $P = .048$, respectively). Other toxicities of maintenance vinorelbine were not statistically significantly different according to the type of induction treatment.

Response in the Maintenance Chemotherapy Arm

Of the 91 patients in the vinorelbine arm, four patients died before evaluation, two refused evaluation, and data were missing for two patients, leaving 83 patients evaluable for response. Ten of the 91 patients (11%) achieved a complete response (six patients with stage IIIB disease and four with stage IV disease) (Table 4). A partial response was seen in 38 of the 91 patients (42%) (21 patients with stage IIIB disease and 17 with stage IV disease). Among these 38 partial responders, eight (three stage IIIB patients and five stage IV patients) improved partial responses (i.e. a substantial reduction in tumor size in a patient in whom lesions persisted) that did not achieve complete response were observed. Progression occurred in 35 (38%) of the 91 patients in the vinorelbine arm.

Table 3. Toxicity of maintenance vinorelbine*

Grade 3–4 toxicities	Vinorelbine after induction chemotherapy, *N* (%)†	Vinorelbine after induction chemoradiation, *N* (%)
Anemia	5 (10)	3 (8)
Leukopenia	18 (36)	22 (60)‡
Thrombocytopenia	2 (4)	1 (3)
Infection	3 (6)	8 (22)§
Hemorrhage	0	1 (3)
Ileus	2 (4)	1 (3)
Pulmonary	3 (6)	3 (8)
Peripheral neuropathy	3 (6)	3 (8)
Cardiac	0	1 (3)
Others	4 (8)	4 (11)
Total‖	50 (100)	37 (100)

*Of the 91 patients in the vinorelbine arm, two patients did not receive vinorelbine (one patient refused and one died of intercurrent cause), and data on toxicity of maintenance vinorelbine were not available for two patients. Thus, toxicity data are presented for 87 patients.

†The patients treated with induction chemotherapy included 47 stage IV patients and 3 stage IIIB patients.

‡$P = .05$, two-sided exact Fisher test.

§$P = .048$, two-sided exact Fisher test. For all other toxicities, there were no differences according to induction treatment.

‖Numbers for individual toxicities do not sum to total because some patients who received induction therapy did not have any grade 3–4 toxicities and some patients who received induction chemoradiation had more than one.

Table 4. Response to maintenance vinorelbine*

	Stage IIIB (improvement of response)	Stage IV (improvement of response)
No. evaluable	38	45
Complete response	6 (3†)	4 (2†)
Partial response	21 (3‡)	17 (5‡)
Progression	11	24

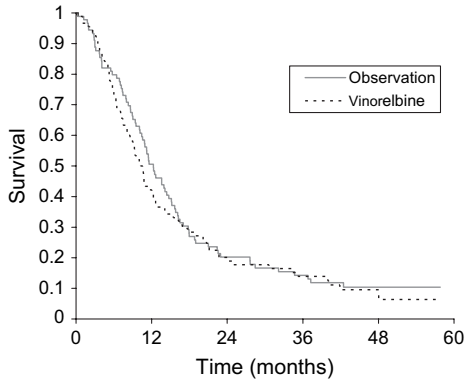
*Of the 91 patients in the vinorelbine arm, four patients died before evaluation, two refused evaluation, and data were missing for two patients. The remaining 83 patients were evaluable for response to maintenance vinorelbine.

†The numbers in parentheses correspond to the patients among the complete responders to maintenance vinorelbine who improved their response with maintenance vinorelbine, i.e., who had a partial response after induction treatment and achieved a complete response with maintenance vinorelbine.

‡The numbers in parentheses correspond to the patients among the partial responders to maintenance vinorelbine who improved their response with maintenance vinorelbine, but without achieving a complete response.

Survival Comparisons

Median follow-up from the date of randomization was 10.4 months (range = 0.07–89.4) in the vinorelbine arm and 11.9 months (range = 0.3–91.7) in the observation arm. The hazard ratio of overall survival, after adjustment for stage, in the vinorelbine arm relative to the observation arm was 1.08 (95% CI = 0.79 to 1.47; $P = .65$). Median survival from the date of randomization was 12.3 months in both the vinorelbine and observation groups. The 1-year, 18-month, and 2-year survival rates were 42%, 28%, and 20% in the vinorelbine group and 51%, 27%, and 20% in the observation group, respectively (log-rank $P = .48$) (Fig. 3). Among stage IIIB patients, 1- and 2-year survival rates were 49% and 22% in the vinorelbine group and 49% and 28% in the observation group, respectively. Among



Survival (months)		0	12	24	36	48	60	P*
Observation	Patients at risk	90	45	18	12	7	4	0.48
	No. events	0	44	71	76	79	80	
Vinorelbine	Patients at risk	91	38	17	11	3	1	
	No. events	0	52	71	76	79	81	

*Two-sided log-rank test

Fig. 3. Kaplan–Meier curves for survival from the date of random assignment by maintenance treatment.

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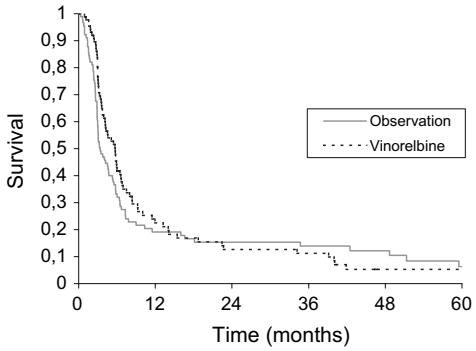

Progression-free survival (months)		0	12	24	36	48	60	P*
Observation	Patients at risk	90	15	12	10	7	3	0.32
	No. events	0	71	74	75	76	79	
Vinorelbine	Patients at risk	91	16	9	8	1	1	
	No. events	0	63	71	71	75	75	

*two-sided log-rank test

Fig. 4. Kaplan–Meier curves for progression-free survival from the date of random assignment by maintenance treatment.

stage IV patients, 1- and 2-year survival rates were 36% and 18% in the vinorelbine group and 53% and 11% in the observation group, respectively. The hazard ratio of progression-free survival, after adjustment for stage, was 0.77 (95% CI = 0.56 to 1.07; $P = .11$). Median progression-free survival from the date of randomization was 5 months in the vinorelbine group and 3 months in the observation group. The 1-year, 18-month, and 2-year progression-free survival rates were 23%, 16%, and 13% in the vinorelbine group and 19%, 16%, and 15% in the observation group, respectively (log-rank $P = .32$) (Fig. 4).

Discussion

The results of this randomized phase III clinical trial indicate that vinorelbine given as maintenance chemotherapy after induction chemotherapy with MIC or induction chemoradiation with MIC followed by thoracic radiation did not improve overall or progression-free survival of patients with advanced NSCLC. Although the trial was stopped early because of slow accrual, its statistical power of 80% provides a strength comparable to that of many clinical studies and is sufficient to rule out the efficacy of maintenance vinorelbine. The inclusion of the responders who were not randomly assigned (mostly because they refused) would have increased the power of the study only slightly.

The toxicity of maintenance vinorelbine seemed to be higher than that of vinorelbine given to chemotherapy-naive patients in phase III trials comparing vinorelbine with vinorelbine–cisplatin *(10,11)*. In our study, the toxicity of maintenance vinorelbine led to treatment being stopped in 21% of patients on the maintenance chemotherapy arm, whereas treatment had to be stopped for toxicity in only 8% of chemotherapy-naive patients treated with single-agent vinorelbine in the phase III setting *(10)*. As typically reported with single-agent vinorelbine, the main toxicity was hematologic. With single-agent vinorelbine in the chemotherapy-naive patients included in phase III trials, treatment-related deaths were reported in 1% of patients, grade 3 and 4 leukopenia in 10% of patients, sepsis requiring hospitalization in 4.3% of patients; no pulmonary toxicity was observed *(10,11)*. With maintenance vinorelbine in the present study, treatment-related deaths also occurred in 1% of patients, but rates of grade 3 and 4 leukopenia, sepsis, and pulmonary toxicity were higher (35.4%, 6.2%, and 6.2% of patients after induction MIC, respectively; 59.5%, 21.6%, and 8.1% after chemoradiation, respectively).

Our choice of MIC as the induction regimen probably played a role in increasing the toxicity of maintenance vinorelbine. Indeed, in our study MIC-related toxicity (leukopenia, thrombocytopenia, and pulmonary toxicity) was more frequent than that reported with other first-line combinations such as vinorelbine–cisplatin, especially when sequential radiotherapy was associated *(10,11)*. However, whatever cytotoxic agents are given, there is a cumulative toxicity of prolonged chemotherapy. In a study comparing three cycles of MVP (mitomycin, vinblastine, and cisplatin) with six or more cycles of the same regimen in 308 patients with advanced NSCLC, anemia and fatigue were statistically significantly increased in patients treated with six courses *(12)*. In a similar study, 230 patients with stage IIIB or IV NSCLC were randomly assigned to receive either four cycles of carboplatin–paclitaxel or continuous carboplatin–paclitaxel until progression. Statistically significantly more peripheral neuropathy was observed in patients on the continuous therapy arm *(13)*.

In our study, the increased toxicity of vinorelbine delivered in the maintenance setting did not result in reduced vinorelbine delivery. Indeed, the mean duration and the median delivered dose intensity of maintenance vinorelbine therapy were similar to those reported previously for vinorelbine given to chemotherapy-naïve patients (in our study, these were 13.8 weeks and 23 $mg \cdot m^{-2} \cdot wk^{-1}$, respectively; with front-line single-agent vinorelbine they were 14 weeks and 22.5 $mg \cdot m^{-2} \cdot wk^{-1}$, respectively) *(10,11)*. Therefore, the increased toxicity of maintenance vinorelbine is probably not responsible for the absence of a survival advantage in the present study.

Both published studies addressing the issue of treatment duration demonstrated no survival benefit of prolonged chemotherapy *(12,13)*. Another phase III study, which compared three to six cycles of carboplatin plus vinorelbine in 297 eligible patients, showed no difference in survival *(14)*. However, there were two major differences in study design between these trials and ours. The first difference concerns eligibility of patients for random assignment to maintenance chemotherapy. In the three other studies, patients were randomly assigned from the beginning of induction chemotherapy, whereas in the trial described here, based on small-cell lung cancer experience, only patients who responded to induction chemotherapy were randomly assigned to maintenance vinorelbine. Although numerous phase II studies of second-line chemotherapy with different agents have been published, whether the response to first-line chemotherapy influences the response to second-line therapy is not clear. Several phase II studies have found no difference in response rates to second-line therapy between patients who responded to first-line cisplatin-based chemotherapy and those who did not *(15–18)*. If maintenance chemotherapy is of any use to patients with NSCLC, it is unlikely to be applicable to all patients, but it is not obvious whether responders are effectively the best candidates. Only a few patients improved their response from a partial to a complete response in the present study, and further reduction of tumor volume in partial responders has never been shown to improve survival. If one considers the fact that objective response is a favorable prognostic factor *(19,20)*, it is conceivable that patients with stable disease after induction chemotherapy might benefit from maintenance

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chemotherapy if they can achieve a response with the maintenance treatment. In a randomized phase II study comparing three different schedules of carboplatin–paclitaxel in 401 patients with stage IIIB or IV NSCLC, the 130 patients who had a response or stable disease after the initial carboplatin–paclitaxel treatment were randomly assigned to receive further paclitaxel treatment until progression or to observation *(21)*. Although that study was not designed to test the efficacy of maintenance chemotherapy, the results were encouraging, with 1- and 2-year survival rates of 72% and 32% in the maintenance paclitaxel arm and of 60% and 26% in the observation arm. The results of a phase III study of maintenance gemcitabine versus observation in 206 patients with a response or stable disease conducted in Eastern Europe are awaited *(22)*.

The second study design consideration is related to the choice of the maintenance drug. The three previously cited phase III trials addressing the question of treatment duration showed that prolongation of the same chemotherapy was of no clinical benefit *(12–14)*. In the present study, to allow the early delivery of an additional cytotoxic agent, a drug different from those given as induction treatment was chosen for maintenance chemotherapy. When this study was designed, in 1993, vinorelbine was the only drug available among a now-larger group of single-agent chemotherapy treatments with attractive therapeutic indexes. Vinorelbine has now been reported to have poor activity in the second-line setting, with no responses observed in two phase II studies of patients with NSCLC *(23,24)* and two responses among 10 patients in a third such study *(25)*. It appears that docetaxel may be a better choice for second-line chemotherapy. Indeed, in a phase III study comparing vinorelbine or ifosfamide versus docetaxel at 75 or 100 $mg \cdot m^{-2}$ every 3 weeks as second-line chemotherapy for patients with advanced NSCLC, response rate was 0.8% for the patients treated with vinorelbine or ifosfamide, 6.7% for those treated with the lower dose of docetaxel ($P = .036$ versus vinorelbine/ifosfamide), and 10.8% for those treated with the higher dose of docetaxel ($P = .001$ versus vinorelbine–ifosfamide) *(26)*. In the same study, 1-year survival rates were 19%, 32%, and 21%, respectively ($P = .025$ for vinorelbine–ifosfamide versus docetaxel at 75 $mg \cdot m^{-2}$). In another phase III trial, in which second-line therapy with docetaxel was compared with best supportive care for patients with advanced NSCLC, 1-year survival in docetaxel-treated patients was 29% compared with 12% in the control group ($P = .047$) *(27)*. Response rates of 0%–38% have been reported for patients with advanced NSCLC treated with second-line paclitaxel and of 0%–21% for those treated with second-line gemcitabine *(28)*.

The consistent results with docetaxel given as second-line treatment suggest that it should be tested in the maintenance setting. Targeted agents are also worth testing as maintenance therapy. Indeed, in patients with NSCLC progressing after treatment with one or more platinum-based chemotherapy regimens, response rates of 12%–18.4% were observed in patients treated with 250 mg of gefitinib daily in the IDEAL phase II studies *(29,30)*. Erlotinib has been reported to statistically significantly improve outcome compared with best-supportive care in second- and third-line treatment of patients with advanced NSCLC *(31)*. The Southwest Oncology Group is currently conducting a phase III trial of maintenance gefitinib versus placebo after concurrent cisplatin–etoposide and radiotherapy plus consolidation chemotherapy with docetaxel in unresectable stage III NSCLC.

In conclusion, the trial described in this article—the first, to our knowledge, to study maintenance chemotherapy with a drug different from that delivered as induction in advanced NSCLC—showed that maintenance vinorelbine did not improve the outcome of responding patients. Maintenance therapy may not be of use for patients with advanced NSCLC. However, other chemotherapeutic agents, especially docetaxel and targeted agents, should be evaluated before the concept is abandoned.

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Notes

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