

ORIGINAL ARTICLE

Vinorelbine plus Cisplatin vs. Observation in Resected Non–Small-Cell Lung Cancer

Timothy Winton, M.D., Robert Livingston, M.D., David Johnson, M.D., James Rigas, M.D., Michael Johnston, M.D., Charles Butts, M.D., Yvon Cormier, M.D., Glenwood Goss, M.D., Richard Inculet, M.D., Eric Vallieres, M.D., Willard Fry, M.D., Drew Bethune, M.D., Joseph Ayoub, M.D., Keyue Ding, Ph.D., Lesley Seymour, M.D., Ph.D., Barbara Graham, R.N., Ming-Sound Tsao, M.D., David Gandara, M.D., Kenneth Kesler, M.D., Todd Demmy, M.D., and Frances Shepherd, M.D., for the National Cancer Institute of Canada Clinical Trials Group and the National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators

ABSTRACT

BACKGROUND

We undertook to determine whether adjuvant vinorelbine plus cisplatin prolongs overall survival among patients with completely resected early-stage non–small-cell lung cancer.

METHODS

We randomly assigned patients with completely resected stage IB or stage II non–small-cell lung cancer to vinorelbine plus cisplatin or to observation. The primary end point was overall survival; principal secondary end points were recurrence-free survival and the toxicity and safety of the regimen.

RESULTS

A total of 482 patients underwent randomization to vinorelbine plus cisplatin (242 patients) or observation (240); 45 percent of the patients had pathological stage IB disease and 55 percent had stage II, and all had an Eastern Cooperative Oncology Group performance status score of 0 or 1. In both groups, the median age was 61 years, 65 percent were men, and 53 percent had adenocarcinomas. Chemotherapy caused neutropenia in 88 percent of patients (including grade 3 febrile neutropenia in 7 percent) and death from toxic effects in two patients (0.8 percent). Nonhematologic toxic effects of chemotherapy were fatigue (81 percent of patients), nausea (80 percent), anorexia (55 percent), vomiting (48 percent), neuropathy (48 percent), and constipation (47 percent), but severe (grade 3 or greater) toxic effects were uncommon (<10 percent). Overall survival was significantly prolonged in the chemotherapy group as compared with the observation group (94 vs. 73 months; hazard ratio for death, 0.69; $P=0.04$), as was relapse-free survival (not reached vs. 46.7 months; hazard ratio for recurrence, 0.60; $P<0.001$). Five-year survival rates were 69 percent and 54 percent, respectively ($P=0.03$).

CONCLUSIONS

Adjuvant vinorelbine plus cisplatin has an acceptable level of toxicity and prolongs disease-free and overall survival among patients with completely resected early-stage non–small-cell lung cancer.

From the National Cancer Institute of Canada Clinical Trials Group, Kingston, Ont. (T.W., M.J., C.B., Y.C., G.G., R.I., D.B., J.A., K.D., L.S., B.G., M.-S.T., F.S.); Southwest Oncology Group, San Antonio, Tex. (R.L., E.V., D.G.); Eastern Cooperative Oncology Group, Boston (D.J., W.F., K.K.); and Cancer and Leukemia Group B, Chicago (J.R., T.D.). Address reprint requests to Dr. Winton at 2D2.09 Walter Mackenzie Health Sciences Centre, University of Alberta Hospital, 8440 112th St., Edmonton, AB T6G 2B7, Canada, or at twinton@cha.ab.ca.

N Engl J Med 2005;352:2589-97.

Copyright © 2005 Massachusetts Medical Society.

LUNG CANCER IS THE LEADING CAUSE OF death from cancer in North America.¹ For early-stage non–small-cell lung cancer, surgical resection is the treatment of choice, yet five-year survival ranges from only 30 percent to 60 percent.² Recurrences leading to death occur mainly in extrathoracic sites after complete resection. Therefore, there is a need for effective systemic therapy to reduce the risk of recurrence and improve survival.^{2,3}

A British Medical Research Council meta-analysis of cisplatin-based chemotherapy after surgery for stage I through stage III non–small-cell lung cancer showed a 13 percent reduction in the risk of death and an absolute improvement in survival of 5 percent at five years, but when compared with observation alone after surgery, the difference was statistically insignificant ($P=0.08$).⁴ More recently, a large international trial of adjuvant chemotherapy that used cisplatin plus either a vinca alkaloid or etoposide (International Adjuvant Lung Cancer Trial [IALT]) reported similar results, with a 4.1 percent improvement in five-year survival (hazard ratio, 0.86; $P<0.03$).⁵ With such small gains in survival, neither physicians nor their patients have been convinced that the toxicity of adjuvant chemotherapy is justified in the treatment of non–small-cell lung cancer. Thus, observation alone has been the standard of care after resection of early-stage non–small-cell lung cancer.

Newer chemotherapeutic agents (vinorelbine, gemcitabine, taxanes, and camptothecins), when coupled with a platinum derivative, have significantly increased response and overall survival rates as compared with previous regimens in advanced non–small-cell lung cancer.^{6,7} Trials confirming the superior efficacy of vinorelbine in combination with platinum as compared with previous combinations were published in the early 1990s.^{6,7} Simultaneously, serotonin-receptor antagonists were shown to be effective in reducing the severity of cisplatin-induced emesis.⁸ Thus, an outpatient regimen of vinorelbine plus cisplatin as adjuvant chemotherapy, administered with antiemetics and supportive care, was considered an excellent choice and led to the initiation of the National Cancer Institute of Canada Clinical Trials Group JBR.10 trial in patients with completely resected stage IB or stage II non–small-cell lung cancer.

METHODS

STUDY DESIGN

This study was a North American intergroup, phase 3, randomized trial of adjuvant vinorelbine plus cisplatin after resection of stage IB or stage II non–small-cell lung cancer. It was begun in April 1994 in Canada. The American cooperative groups (Cancer and Leukemia Group B [CALGB], Southwest Oncology Group [SWOG], and Eastern Cooperative Oncology Group [ECOG]) joined in 1998. Within six weeks after surgery, eligible patients were randomly assigned in a 1:1 ratio⁹ to adjuvant vinorelbine plus cisplatin or observation. Patients were stratified according to nodal status (N0 vs. N1) and the presence or absence of a *ras* mutation. The primary end point was overall survival. Secondary end points included recurrence-free survival and the safety, toxicity, and quality of life associated with this regimen.

The protocol was approved by the institutional review boards at all the institutions, and all patients provided written informed consent. Funding was provided by the National Cancer Institute of Canada, the National Cancer Institute of the United States, and GlaxoSmithKline. Data were collected, managed, and analyzed by the National Cancer Institute of Canada Clinical Trials Group. GlaxoSmithKline had no part in writing the manuscript but did review an early draft, with no right to change the text or its conclusions. There was no contractual obligation with GlaxoSmithKline with respect to the decision to submit the manuscript for publication, and the company had no influence on the content or preparation of this article. Dr. Winton, the study chair, vouches for the accuracy and completeness of the data.

ELIGIBILITY CRITERIA

Patients 18 years of age or older with completely resected T2N0, T1N1, or T2N1 non–small-cell lung cancer with acceptable baseline characteristics and an ECOG performance status of 0 or 1 were eligible. All patients had a preoperative computed tomographic scan, and intraoperative mediastinal lymph-node resection or biopsy of nodes that were 1.5 cm or larger was mandatory. Patients with incomplete preoperative or intraoperative staging, incomplete resection, wedge or segmental resec-

tion, involvement of tracheobronchial angle nodes (station 10) or more central mediastinal nodes, mixed histologic features, a T3 tumor, or diffuse lobar or multifocal bronchioalveolar carcinoma and patients who had had breast cancer, renal-cell carcinoma, melanoma, or other cancers treated within the previous five years were ineligible. Patients with clinically significant cardiac dysfunction, active infection, or neurologic or psychiatric disorders were also ineligible.

RANDOMIZATION AND TREATMENT REGIMEN

Treatment started within two days after randomization. A regimen of 50 mg of cisplatin per square meter of body-surface area on days 1 and 8 every 4 weeks for four cycles and 25 mg of vinorelbine per square meter weekly for 16 weeks was prescribed. The protocol originally called for 30 mg of vinorelbine per square meter, but the dose was amended in August 1995 because of hematologic toxicity (only 18 patients received 30 mg of vinorelbine per square meter). All patients received ondansetron, commonly with a corticosteroid, and chemotherapy was adjusted for toxicity according to protocol guidelines.

FOLLOW-UP

Follow-up clinical examinations and chest radiography were performed every three months for three years and every six months thereafter. Data assessing quality of life were collected prospectively in both groups, but the details of the findings and data analysis are beyond the scope of this article.

ras EVALUATION

Participating centers submitted fresh-frozen primary tumor or paraffin-embedded blocks of tissue specimens to a central laboratory for *ras* mutation analysis of codons 12, 13, and 61 of the *H-ras*, *K-ras*, and *N-ras* genes by allele-specific oligonucleotide hybridization. The results were confirmed by sequencing.¹⁰

STATISTICAL ANALYSIS

A sample size of 450 patients recruited over a period of 6.75 years, with less than 1 year of follow-up, and 198 events (deaths) were required to provide the study with 80 percent power to detect a 10 percent improvement in survival (from an estimated 3-year survival rate of 60 percent) with a one-sided

5 percent significance level. Two planned interim analyses were conducted in March 2000 and March 2002, after 64 and 122 deaths, respectively. The database was locked in April 2004, and all randomized patients were included in the final analysis, which was based on the intention-to-treat method. Patients who received any protocol treatment were included in toxicity analyses.

Median survival, 95 percent confidence intervals, and Kaplan–Meier estimates of recurrence-free survival and overall survival were calculated according to standard methods.^{11–13} The Cox regression model, stratified according to nodal status — including the status of *ras* mutations (unknown vs. mutation vs. wild type) as a covariate — was used to test the difference in overall and recurrence-free survival between the study groups.¹³ For the primary analysis of overall survival, the stagewise ordering method was used to obtain the P value adjusted for the two planned interim analyses.¹⁴ An unadjusted log-rank test and an exploratory, stratified Cox regression model analysis, adjusted for *ras* status, age, sex, performance status (ECOG 0 or 1), extent of resection, and histologic features, were performed. To test whether treatment effects were homogeneous across the stratification factors, subgroup analyses of overall and recurrence-free survival with the use of proportional-hazards models with interaction terms were included.¹³ All P values reported are the result of two-sided tests.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between July 1994 and April 2001, 532 patients were registered, and 482 were randomly assigned to observation (240 patients) or chemotherapy (242). Fifty registered patients (9.4 percent) never underwent randomization, owing to patient refusal (36 patients), postoperative death (2), intercurrent illness (4), decreased performance status (2), metastases (2), and ineligibility (4). Forty-one patients (8.5 percent) — 22 in the observation group and 19 in the chemotherapy group — who underwent randomization did not fully meet eligibility criteria: 7 had incomplete staging or screening data, 15 had tumors that were more advanced than stage II, 18 had abnormal laboratory results, and 1 had incomplete resection.

Follow-up ranged from 1.5 to 9.3 years (median,

5.1 years) in the chemotherapy group and 0.4 to 9.0 years (median, 5.3 years) in the observation group. Three patients (0.6 percent) were lost to follow-up, two in the treatment group at 6.3 and 7.0 years after randomization and one in the observation group at 4.1 years after randomization.

The baseline characteristics of the patients are shown in Table 1. The two groups were evenly distributed with respect to important prognostic variables, including age, sex, ECOG performance status, and histologic features.

Table 1. Baseline Characteristics of the Randomized Patients.

Characteristic	Observation (N=240)	Chemotherapy (N=242)
Age (yr)		
Median	61	61
Range	34–78	35–82
Male sex (%)	64	66
ECOG performance status (%)*		
0	49	50
1	51	50
Histologic features (%)		
Adenocarcinoma	53	53
Squamous	38	37
Undifferentiated	7	8
Mixed	2	2
<i>ras</i> status (%)		
Mutation present	24	24
Wild type	70	68
Unknown	6	8
Pathological tumor stage (%)		
1	13	16
2	87	84
Nodal status (%)		
0	45	46
1	55	54
Stage (%)		
IB	45	46
IIA	13	16
IIB	42	38
Extent of resection (%)		
Lobectomy	71	66
Bilobectomy	7	9
Pneumonectomy	22	25

* ECOG denotes Eastern Cooperative Oncology Group.

DELIVERY AND TOXICITY OF CHEMOTHERAPY

Data concerning drug delivery, treatment compliance, and quality of life were reported previously.^{15,16} At least one dose of medication was received by 231 patients (95.5 percent); 11 of the patients randomly assigned to vinorelbine plus cisplatin (4.5 percent) did not receive chemotherapy (9 patients refused treatment, 1 was ineligible, and 1 was randomly assigned to observation erroneously) (Table 2). The median number of cycles delivered was three. Fifty-eight percent of the patients received three or more cycles of cisplatin, 77 percent had at least one dose reduction or omission, and 55 percent required one dose delay or more, most related to neutropenia at the expected time of vinorelbine administration on day 15 (cycle week 3). Seventy-three of the patients who received at least one dose (32 percent) required hospitalization — 16 (7 percent) for administration of chemotherapy, 14 (6 percent) for reasons unrelated to treatment (with death in 1 patient), and 43 (19 percent) for medical problems related to toxicity (with death in 1 patient).

Neutropenia was the most common severe toxic effect of chemotherapy; 73 percent of patients had grade 3 or 4 neutropenia, 7 percent had grade 3 or 4 anemia, and 1 percent had grade 3 thrombocytopenia (Table 3). Colony-stimulating factors were administered to 15 percent of the patients and febrile neutropenia occurred in 7 percent. Severe non-hematologic toxic effects from chemotherapy were uncommon. Grade 3 or 4 anorexia, nausea, or vomiting was reported by 10 percent, 10 percent, and 7 percent of the patients, respectively. Grade 3 or 4 sensory neurotoxicity, motor neurotoxicity, or hearing loss was observed in 2 percent, 3 percent, and 2 percent, respectively.

Two patients (0.8 percent) died because of treatment-related toxicity — one during chemotherapy from sepsis secondary to febrile neutropenia, and one six months after chemotherapy from interstitial lung disease, first documented during treatment.

RELAPSE-FREE AND OVERALL SURVIVAL

Recurrence was documented in 206 patients (42.7 percent) — 87 in the group assigned to vinorelbine and cisplatin (36.0 percent) and 119 in the observation group (49.6 percent) ($P=0.003$). The Kaplan-Meier estimates of recurrence-free survival are shown in Figure 1A. Chemotherapy significantly prolonged recurrence-free survival as compared with observation (hazard ratio for recurrence, 0.60; 95 percent confidence interval, 0.45 to 0.79;

Table 2. Delivery of Chemotherapy for Patients Randomly Assigned to Vinorelbine plus Cisplatin.

Delivery Status*	Total No. of Patients	Percent Randomized (N=242)	Percent Treated (N=231)
Randomized	242	100	96
Never treated	11	4	
Day 1 of cycle 1 only	27	11	12
Completed at least cycle 1	204	84	88
Completed cycle 2	156	64	68
Completed cycle 3	133	55	58
Completed cycle 4	110	45	48

* A completed cycle indicates that the patient received both planned doses of cisplatin for that cycle.

$P < 0.001$). The median recurrence-free survival was 46.7 months in the observation group and had not been reached in the chemotherapy group at the time the database was locked. The five-year recurrence-free survival rates were 61 percent (95 percent confidence interval, 54 to 68 percent) in the vinorelbine-cisplatin group and 49 percent (95 percent confidence interval, 42 to 55 percent) in the observation group ($P = 0.08$). Use of the stratified Cox regression model showed that only chemotherapy ($P < 0.001$) and squamous histologic features ($P = 0.002$) were associated with significantly prolonged recurrence-free survival.

A total of 197 patients (111 in the observation group and 86 in the chemotherapy group) had died when the database was locked. Eighty-two percent of them died from recurrent lung cancer (92 in the observation group and 70 in the chemotherapy group), 5 percent from second malignant conditions (5 and 4, respectively), and 12 percent from other causes (11 and 13, respectively). Of the 11 patients in the observation group who died from other causes, 6 died from myocardial infarction, 2 from pulmonary emboli, 2 from an exacerbation of chronic obstructive pulmonary disease, and 1 from a ruptured aortic aneurysm. Of the 13 patients in the vinorelbine-cisplatin group who died from other causes, 6 died from myocardial infarction, 2 from pulmonary emboli, 1 from chronic obstructive pulmonary disease, 1 from gastrointestinal bleeding, 1 from stroke, and 2 from alcohol toxicity.

Figure 1B shows Kaplan-Meier estimates of overall survival. The median survival after chemotherapy was significantly prolonged, at 94 months

Table 3. Drug-Related Adverse Events among Patients Who Received at Least One Dose of Vinorelbine plus Cisplatin.

Adverse Event	Vinorelbine plus Cisplatin*	
	Any Grade	Grade 3 or 4 percent
General		
Fatigue	81	15
Anorexia	55	10
Alopecia	32	0
Local toxicity	35	3
Gastrointestinal		
Diarrhea	23	<1
Nausea	80	10
Vomiting	48	7
Constipation	47	3
Infectious		
Infection	22	1
Febrile neutropenia	7	7†
Neurotoxic		
Hearing loss	21	2
Sensory neuropathy	48	2
Motor neuropathy	15	3
Respiratory		
Dyspnea	18	4
Hematologic		
Thrombocytopenia	32	1
Anemia	93	7
Neutropenia	88	73
Biochemical		
ALT elevation‡	18	<1
Bilirubin elevation	4	<1
Creatinine elevation	16	<1

* Toxicity was graded and reported according to expanded criteria of the National Cancer Institute of Canada Clinical Trials Group.^{15,16} The percent denotes the percentage of the 231 patients who received at least one dose of the protocol treatment.

† Six percent had febrile neutropenia after the dose of vinorelbine was reduced.

‡ ALT denotes alanine aminotransferase.

(95 percent confidence interval, 73 to not reached), as compared with 73 months (95 percent confidence interval, 48 to not reached) in the observation group (hazard ratio, 0.69; 95 percent confidence interval, 0.52 to 0.91; $P = 0.009$; $P = 0.04$ after adjustment for interim analyses). There was an absolute survival advantage of 15 percentage points at

five years — 69 percent (95 percent confidence interval, 62 to 75 percent) in the vinorelbine–cisplatin group and 54 percent (95 percent confidence interval, 48 to 61 percent) with observation alone ($P=0.03$).

Subgroup analyses according to stratification factors did not show a statistically significant improvement in overall survival among patients with stage IB non–small-cell lung cancer in the chemotherapy group as compared with the observation group ($P=0.79$) (Fig. 1C). The median survival among patients with stage II non–small-cell lung cancer was 41 months in the observation group and 80 months in the chemotherapy group (hazard ratio, 0.59; 95 percent confidence interval, 0.42 to 0.85; $P=0.004$) (Fig. 1D). These findings must be considered with caution, given that no statistically significant effect of treatment according to disease stage was detected ($P=0.13$).

The status of *ras* mutations in the tumors is known in 450 patients (93 percent). The median survival among patients with wild-type *ras* in the observation group was 74 months and had not been reached in the group that received chemotherapy (hazard ratio, 0.69; 95 percent confidence interval, 0.49 to 0.98; $P=0.03$). In contrast, adjuvant chemotherapy did not seem to confer a survival advantage in patients whose tumors had *ras* mutations (hazard ratio, 0.95; 95 percent confidence interval, 0.53 to 1.71; $P=0.87$). However, in the interaction analysis, the effect of the status of *ras* mutations on the outcome of treatment was not statistically significant ($P=0.29$).

In the planned stratified Cox regression analysis, significant factors that were associated with improved survival included chemotherapy as compared with observation (hazard ratio for the difference in survival, 0.67; 95 percent confidence interval, 0.51 to 0.89; $P=0.006$) and squamous histologic features as compared with adenocarcinomas ($P=0.005$). In contrast, older age ($P=0.001$), male sex ($P=0.03$), and pneumonectomy as compared with lesser resection ($P=0.02$) were associated with shorter survival; *ras* mutation was not a predictor of survival.

DISCUSSION

This prospective, randomized trial documents the benefit of adjuvant vinorelbine plus cisplatin in completely resected, early-stage non–small-cell lung cancer. The overall survival advantage at five

years was 15 percentage points ($P=0.03$), exceeding the marginal benefit (5 percentage points) observed in the British Medical Research Council meta-analysis⁴ and the large IALT trial, which reported a survival advantage of 4.1 percentage points at five years ($P<0.03$).⁵

Three other trials of adjuvant chemotherapy for non–small-cell lung cancer undertaken during the past decade have been reported. Keller et al.¹⁷ reported the results of the ECOG trial of adjuvant etoposide plus cisplatin and radiotherapy as compared with radiotherapy alone after resection of stage II or IIIA non–small-cell lung cancer. There was no difference between the groups in the recurrence rate or in survival, and greater toxicity was observed in the chemoradiotherapy group in this trial. Similarly, the Adjuvant Lung Project Italy (ALPI)¹⁸ found no benefit from three cycles of mitomycin C, vindesine, and cisplatin in 1209 patients with stage I to IIIA non–small-cell lung cancer. Finally, Waller et al.¹⁹ (of the Big Lung Trial) reported that 381 patients with non–small-cell lung cancer who were randomly assigned to various platinum-based regimens in a neoadjuvant or adjuvant setting had no benefit from treatment.

What accounts for the results of the current trial? Several important factors should be considered. The superiority of the vinorelbine–cisplatin combination has been well established in patients with advanced non–small-cell lung cancer, in whom it has been shown to provide significantly better response rates and overall survival than other regimens.^{7,20–26} With the exception of IALT⁵ and the Big Lung Trial,¹⁹ in which only 27 percent and 22 percent of patients, respectively, received vinorelbine plus cisplatin, all the negative trials used older chemotherapeutic combinations with comparatively less efficacy in advanced non–small-cell lung cancer.

The CALGB protocol 9633 trial, in which another current adjuvant regimen (paclitaxel plus carboplatin) was compared with observation alone after complete resection of stage IB non–small-cell lung cancer, found a similar improvement in survival rates (an improvement of 12 percentage points at four years, vs. 15 percentage points at five years in the current trial) and a similar, significant reduction in the risk of death from recurrent lung cancer.²⁷ Vinorelbine plus cisplatin and paclitaxel plus carboplatin have similar efficacy in advanced non–small-cell lung cancer²²; hence, it is not surprising that they have been found to confer similar survival benefits in the adjuvant setting.

All patients in the ECOG trial of adjuvant therapy,¹⁷ and 31 percent and 43 percent of patients in IALT⁵ and the ALPI trial,¹⁸ respectively, received radiotherapy in addition to chemotherapy, with variable delivery of the dosage of radiotherapy between the treatment and observation groups. Radiotherapy may have had a deleterious effect on outcomes, since a meta-analysis of postoperative radiotherapy (known as PORT) showed that the risk of death increased by 21 percent with a 7 percent reduction in two-year survival with postoperative radiation.²⁸ Furthermore, the Medical Research Council meta-analysis of adjuvant radiotherapy with or without

chemotherapy showed no benefit from chemoradiotherapy and no survival benefit from radiotherapy alone.⁴ Finally, the cumulative toxic effects of chemoradiotherapy may limit the delivery of cytotoxic systemic chemotherapy and hence reduce efficacy.

Only patients with early-stage (stage IB or stage II) non-small-cell lung cancer were included in CALGB protocol 9633²⁷ and this trial. Previous trials included significant numbers of patients with resected stage IIIA non-small-cell lung cancer. Patients with stage IIIA disease have a high likelihood of harboring occult extrathoracic disease,

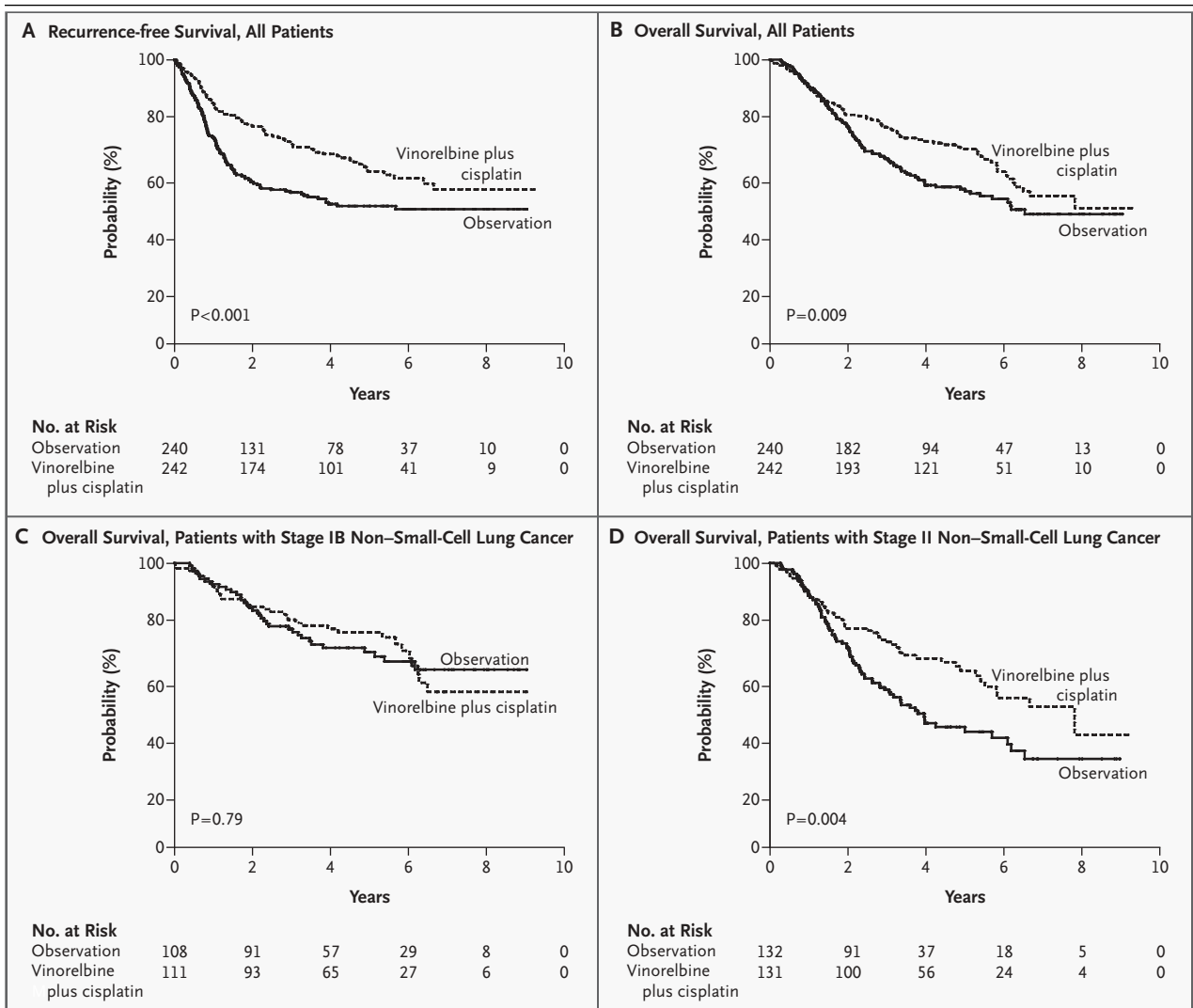


Figure 1. Kaplan–Meier Estimates of Survival among Patients Who Received Adjuvant Vinorelbine plus Cisplatin and Those Who Underwent Observation Alone.

P values are based on two-sided statistical analyses of differences between treatment groups after randomization.

are heterogeneous in terms of the extent (burden or bulk) of disease and number of nodal stations involved, frequently have a poor performance status, often require pneumonectomy, and do not tolerate chemotherapy well.^{2,3,15} These factors may have contributed to the inability of these earlier trials to show a survival benefit from chemotherapy.

Subgroup analyses indicate that the survival advantage in our trial was most prominent in patients with stage II disease. We cannot explain why the benefit in patients with stage IB disease was less and did not reach statistical significance (7 percent benefit at five years, vs. 20 percent among those with stage II disease). The number of patients with stage IB disease was small, the number of events was smaller than had been anticipated when the subgroup analysis was planned, and the statistical test for stage-by-treatment interaction was not significant ($P=0.13$). Therefore, it is important not to place too much emphasis on this subgroup analysis.

Patients with tumors containing *ras* gene mutations have poorer survival after surgery than those without *ras* mutations, but to our knowledge, previous studies have not prospectively examined the status of *ras* genes in relation to survival or the response to adjuvant chemotherapy.²⁹⁻³¹ The observation that patients with *ras* mutations did not benefit from adjuvant chemotherapy, whereas those with wild-type *ras* did, requires further analysis and validation, especially because the secondary analysis for interaction terms failed to show statistically significant differences between the groups ($P=0.29$).

The vinorelbine-cisplatin regimen was associated with acceptable adverse event rates after reduc-

tion of the vinorelbine dose from 30 to 25 mg per square meter weekly. The rates of febrile neutropenia (7 percent) and of treatment-related death (0.8 percent) are similar to the rates of these events in other reports. Cisplatin-based regimens are associated with enhanced efficacy and toxicity as compared with carboplatin-based therapy^{32,33}; yet in CALGB protocol 9633,²⁷ 33 percent of patients required dose reductions, and not all completed a full course of therapy. Our quality-of-life analyses showed that, despite toxicity, the decline in function- and symptom-related domains during chemotherapy in the current trial was limited and resolved rapidly (within three months after completion of therapy).¹⁶

This study indicates that adjuvant treatment with vinorelbine plus cisplatin can be safely administered in the outpatient setting with limited toxicity and is beneficial in non-small-cell lung cancer. We believe that a brief course of such chemotherapy should become the standard of care for patients with good performance status after complete resection of stage IB or stage II non-small-cell lung cancer.

Supported by grants (4493 and 12150) from the Canadian Cancer Society and the National Cancer Institute of Canada and by grants (CA04326 and CA31946, to Drs. Rigas and Demmy) from the National Cancer Institute and Cancer and Leukemia Group B.

We are indebted to the patients who participated in this study; to the trial committee; to the investigators, pharmacists, and clinical research associates from the National Cancer Institute of Canada Clinical Trials Group, SWOG, ECOG, and CALGB; to the members of the Canadian Association for Thoracic Surgery who supported this trial from the outset; to the members of the data safety and monitoring committee; and to the central office staff of the National Cancer Institute of Canada Clinical Trials Group who helped conduct this trial.

REFERENCES

- Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. *CA Cancer J Clin* 2004; 54:8-29.
- Ponn RB, Lo Cicero J III, Daly BDT. Surgical treatment of nonsmall cell lung cancer. In: Shields TW, Lo Cicero III J, Ponn R, Rusch VW, eds. *General thoracic surgery*. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2005:1548-87.
- Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997;111:1710-7.
- 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 randomised clinical trials. *BMJ* 1995;311:899-909.
- The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;350:351-60.
- Shepherd FA. Chemotherapy for non-small-cell lung cancer. In: Pearson FG, Cooper JD, Deslauriers J, et al., eds. *Thoracic surgery*. 2nd ed. New York: Churchill Livingstone, 2002:859-74.
- 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* 1994;12:360-7.
- Italian Group for Antiemetic Research. Ondansetron + dexamethasone vs metoclopramide + dexamethasone + diphenhydramine in prevention of cisplatin-induced emesis. *Lancet* 1992;340:96-9.
- Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trials. *Biometrics* 1975;31:103-15.
- Tsao M-S, Liu N, Nicklee T, Shepherd F, Viallet J. Angiogenesis correlates with vascular endothelial growth factor expression but not with Ki-ras oncogene activation in non-small cell lung carcinoma. *Clin Cancer Res* 1997;3:1807-14.
- Brookmeyer R, Crowley JJ. A confidence interval for median survival time. *Biometrics* 1982;38:29-41.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Tsiatis AA, Rosner GL, Mehta CR. Exact confidence intervals following a group sequential test. *Biometrics* 1984;40:797-803.
- Alam N, Shepherd FA, Winton T, et al. Compliance with post-operative adjuvant chemotherapy in non-small cell lung cancer: an analysis of National Cancer Institute of Canada and intergroup trial JBR.10 and a

review of the literature. *Lung Cancer* 2005; 47:385-94.

16. Beziak A, Winton T, Ding K et al. Quality of life in a trial of adjuvant chemotherapy for early stage completely resected non-small cell lung cancer (NCIC CTG BR.10). *Lung Cancer* 2003;41:Suppl 2:S20. abstract.
17. Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIa non-small-cell lung cancer. *N Engl J Med* 2000;343:1217-22.
18. Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II or IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 2003;95:1453-61.
19. Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *Eur J Cardiothorac Surg* 2004;26:173-82.
20. Cullen M. Chemotherapy for non-small cell lung cancer: the end of the beginning. *Thorax* 2003;58:352-6.
21. Socinski MA, Morris DE, Masters GA, et al. Chemotherapeutic management of stage IV non-small cell lung cancer. *Chest* 2003; 123:Suppl 1:226S-243S.
22. 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* 2001;19: 3210-8.

23. Keller SM, Vangel MG, Adak S, et al. The influence of gender on survival and tumour recurrence following adjuvant therapy of completely resected stages II and IIIa non-small cell lung cancer. *Lung Cancer* 2002; 37:303-9.
24. Bonomi P, Kim K, Fairclough D, et al. Comparison of survival and quality of life in non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group Trial. *J Clin Oncol* 2000;18:623-31.
25. Giaccone G, Splinter TA, Debruyne S, et al. Randomized study of paclitaxel-cisplatin versus cisplatin-teniposide in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 1998;16:2133-41.
26. Bunn PA Jr, Kelly K. New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. *Clin Cancer Res* 1998;4:1087-100.
27. Strauss GM, Herndon J, Maddaus MA, et al. Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in Stage IB non-small cell lung cancer: Report of Cancer and Leukemia Group B (CALGB) Protocol 9633. *J Clin Oncol* 2004;22:Suppl 14S:7019.

28. PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systemic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet* 1998; 352:257-62.

29. Mitsudomi T, Steinberg SM, Oie HK, et al. Ras gene mutations in non-small cell lung cancers are associated with shortened survival irrespective of treatment intent. *Cancer Res* 1991;51:4999-5002.
30. Sugio K, Ishida T, Yokoyama H, Inoue T, Sugimachi K, Sasazuki T. Ras gene mutations as a prognostic marker in adenocarcinoma of the human lung without lymph node metastasis. *Cancer Res* 1992;52:2903-6.
31. Rosell R, Li S, Skacel Z, et al. Prognostic impact of mutated K-ras gene in surgically resected non-small cell lung cancer patients. *Oncogene* 1993;8:2407-12.
32. Zojwalla NJ, Raftopoulos H, Gralla RJ. Are cisplatin and carboplatin equivalent in the treatment of non-small cell lung carcinoma (NSCLC)? Results of a comprehensive review of randomized studies in over 2300 patients. *J Clin Oncol* 2004;22:Suppl 14S: 7068.
33. Soria JC, Le Chevalier T. Is cisplatin still the best platinum compound in non-small-cell lung cancer? *Ann Oncol* 2002;13:1515-7.

Copyright © 2005 Massachusetts Medical Society.

PHYSICIAN-JOURNALIST

The *Journal* is seeking a physician with substantial reporting experience to write occasional articles on timely topics in medicine and society for the Perspective section. Send curriculum vitae and writing samples to Perspective Editor, *New England Journal of Medicine*, 10 Shattuck St., Boston, MA 02115, or at writer@nejm.org.