COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

Joan H. Schiller, M.D., David Harrington, Ph.D., Chandra P. Belani, M.D., Corey Langer, M.D., Alan Sandler, M.D., James Krook, M.D., Junming Zhu, Ph.D., and David H. Johnson, M.D., for the Eastern Cooperative Oncology Group

ABSTRACT

Background   We conducted a randomized study to determine whether any of three chemotherapy regimens was superior to cisplatin and paclitaxel in patients with advanced non–small-cell lung cancer.

Methods   A total of 1207 patients with advanced non–small-cell lung cancer were randomly assigned to a reference regimen of cisplatin and paclitaxel or to one of three experimental regimens: cisplatin and gemcitabine, cisplatin and docetaxel, or carboplatin and paclitaxel.

Results   The response rate for all 1155 eligible patients was 19 percent, with a median survival of 7.9 months (95 percent confidence interval, 7.3 to 8.5), a 1-year survival rate of 33 percent (95 percent confidence interval, 30 to 36 percent), and a 2-year survival rate of 11 percent (95 percent confidence interval, 8 to 12 percent). The response rate and survival did not differ significantly between patients assigned to receive cisplatin and paclitaxel and those assigned to receive any of the three experimental regimens. Treatment with cisplatin and gemcitabine was associated with a significantly longer time to the progression of disease than was treatment with cisplatin and paclitaxel but was more likely to cause grade 3, 4, or 5 renal toxicity (in 9 percent of patients, vs. 3 percent of those treated with cisplatin plus paclitaxel). Patients with a performance status of 2 had a significantly lower rate of survival than did those with a performance status of 0 or 1.

Conclusions   None of four chemotherapy regimens offered a significant advantage over the others in the treatment of advanced non–small-cell lung cancer. (N Engl J Med 2002;346:92-8.)

APPROXIMATELY one third of all cancer-related deaths are due to lung cancer, which accounts for more deaths each year than breast, prostate, and colon cancer combined. The median survival of patients with untreated metastatic non–small-cell lung cancer is only four to five months, with a survival rate at one year of only 10 percent.[1]

Chemotherapy for advanced non–small-cell lung cancer is often considered ineffective or excessively toxic. However, meta-analyses have demonstrated that, as compared with supportive care, chemotherapy results in a small improvement in survival in patients with advanced non–small-cell lung cancer.[2-4] In addition, randomized studies comparing chemotherapy with the "best supportive care" have shown that chemotherapy reduces symptoms and improves the quality of life.[5]

Over the past decade, a number of new agents have become available for the treatment of metastatic non–small-cell lung cancer, including the taxanes, gemcitabine, and vinorelbine. The combination of one or more of these agents with a platinum compound has resulted in high response rates and prolonged survival at one year in phase 2 studies.[6-10] However, there have been few comparisons of these newer chemotherapy regimens, which are now used frequently, with each other.

The Eastern Cooperative Oncology Group (ECOG) conducted a randomized clinical trial to compare the efficacy of three commonly used regimens with that of a reference regimen of cisplatin and paclitaxel.[11] The primary objective of this study was to compare overall survival in patients treated with cisplatin and gemcitabine, cisplatin and docetaxel, carboplatin and paclitaxel, or cisplatin and paclitaxel.

METHODS

Patients with non–small-cell lung cancer that was classified as stage IIIB (with malignant pleural or pericardial effusion), stage IV, or recurrent disease were randomly assigned to one of four treatment groups (Fig. 1). The first group received the reference treatment: 135 mg of paclitaxel per square meter of body-surface area, administered over a 24-hour period on day 1, followed by 75 mg of cisplatin per square meter on day 2. The cycle was repeated every three weeks. In the second group, gemcitabine, at a dose of 1000 mg per square meter, was administered on days 1, 8, and 15, and cisplatin, at a dose of 100 mg per square meter, was administered on day 1 of a four-week cycle. Patients in the third group received 75 mg of docetaxel per square meter and 75 mg of cisplatin per square meter on day 1 of a three-week cycle. Those in the fourth group were treated with 225 mg of paclitaxel per square meter, given over a three-hour period on day 1, followed on the same day by carboplatin at a dose calculated to produce an area

Stratification Variables

Performance status: 0 or 1 vs. 2

Weight loss in previous 6 mo: <5% vs. ≥5%

Disease stage: IIIB vs. IV or recurrent disease

Presence or absence of brain metastases

Regimens

Cisplatin plus paclitaxel

  paclitaxel, 135 mg/m² over 24-hr period on day 1

  cisplatin, 75 mg/m² on day 2

  3-wk cycle

Cisplatin plus gemcitabine

  gemcitabine, 1000 mg/m² on days 1, 8, and 15

  cisplatin, 100 mg/m² on day 1

  4-wk cycle

Cisplatin plus docetaxel

  docetaxel, 75 mg/m² on day 1

  cisplatin, 75 mg/m² on day 1

  3-wk cycle

Carboplatin plus paclitaxel

  paclitaxel, 225 mg/m² over 3-hr period on day 1

  carboplatin, AUC 6.0 mg/ml/min on day 1

  3-wk cycle

Figure 1. Stratification and Randomly Assigned Treatment Regimens.

AUC denotes area under the concentration–time curve.

under the concentration–time curve of 6.0 mg per milliliter per minute, in a three-week cycle. Patients were stratified according to ECOG performance status (0 or 1 vs. 2, with higher scores indicating greater impairment), weight loss in the previous six months (<5 percent vs. ≥5 percent), the stage of disease (IIIB vs. IV or recurrent disease), and the presence or absence of brain metastases.

Eligibility Criteria

Patients who had received prior chemotherapy were ineligible for the study. The criteria for eligibility included confirmed disease, measurable or nonmeasurable; an age of at least 18 years; and adequate hematologic function (as indicated by a white-cell count of at least 4000 per cubic millimeter and a platelet count of at least 100,000 per cubic millimeter), hepatic function (as indicated by a bilirubin level that did not exceed 1.5 mg per deciliter [25.6 μmol per liter]), and renal function (as indicated by a creatinine level that did not exceed 1.5 mg per deciliter [132.6 μmol per liter]). Prior radiation therapy at symptomatic sites was permitted provided that the indicator sites (the sites that were followed to determine whether there was a response) had not been irradiated and that the radiation therapy had been completed before chemotherapy was initiated. Patients with stable brain metastases were eligible. All patients gave informed consent.

Standard ECOG response criteria were used. Briefly, a complete response was defined as the absence of disease at all known sites for at least four weeks. A partial response was defined as a 50 percent reduction in the sum of the perpendicular diameters of all measurable lesions, lasting at least four weeks. Progressive disease was

defined as either a 25 percent increase in the area of any one lesion over the prior measurement or the development of one or more new lesions. Survival was calculated from the date of enrollment to the date of death or the date when the patient was last known to be alive. The time to the progression of disease was calculated from the date of enrollment to the date of progression or death; data for patients who were alive and relapse-free were censored as of the date of the last known follow-up visit.

The protocol was approved by the institutional review board at each participating center. All patients gave written informed consent.

Statistical Analysis

Survival from the date of enrollment was the main end point. The primary analysis specified by the protocol was a comparison of each of the survival distributions for the three experimental-treatment groups with that for the control reference-treatment group, with the use of a two-sided log-rank test.[12] To control for type I error (i.e., to control for multiple comparisons), a nominal two-sided P value of 0.016 was used for each comparison. The study was designed to have 80 percent power to detect a 33 percent increase in median survival in the experimental-treatment groups — that is, a median survival of 12 months, since the reference regimen had resulted in a median survival of 9 months in a previous study.[11] Full power to detect a 33 percent improvement in survival would have required a total of approximately 1070 deaths in the four groups, or 535 per pairwise comparison. On the basis of accrual and eligibility rates in previous ECOG trials, we estimated that we would need to enroll 300 patients per treatment group over a 30-month period.

Interim analyses for the study were monitored by the ECOG Data Monitoring Committee. The design specified two interim analyses and one final analysis of the survival data, with the use of an O'Brien–Fleming boundary,[13] when 33 percent, 67 percent, and 100 percent of the anticipated number of deaths had occurred.

All reported P values are two-sided and were adjusted for interim analyses according to the O'Brien–Fleming method. All time-to-event distributions were estimated by the Kaplan–Meier method.[14] All reported time-to-event comparisons were made with the use of the log-rank test. Categorical data, such as data on treatment, responses, and toxic effects, were compared among treatment groups with the use of Fisher's exact test.[15]

RESULTS

A total of 1207 patients were enrolled in the study between October 1996 and May 1999. The median follow-up period was 8.0 months. As of May 1, 2001, 1074 patients had died. Of the 1207 patients who were enrolled, 52 (4.3 percent) were subsequently found to be ineligible (Table 1).

The clinical characteristics of the patients in the four groups were similar (Table 1). The median age was 63 years. Almost two thirds of the patients were men. Sixty-four percent of patients had a performance-status score of 1, and 13 percent had brain metastases. About two thirds of the patients had a weight loss of less than 5 percent in the previous six months. Most (87 percent) had stage IV or recurrent disease.

The median survival for all 1207 patients was 8.0 months; the survival rate at 1 year was 34 percent, and the rate at 2 years was 12 percent (Table 2). Analyses that compared the total group of 1207 patients with the group of 1155 eligible patients showed no sig-

TABLE 1. CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	CISPLATIN AND PACLITAXEL (N=303)	CISPLATIN AND GEMCITABINE (N=301)	CISPLATIN AND DOCETAXEL (N=304)	CARBOPLATIN AND PACLITAXEL (N=299)	TOTAL (N=1207)
Eligible (no. of patients)	288	288	289	290	1155
Ineligible (no. of patients)*	15	13	15	9	52
Age (yr)					
Median	62	64	63	63	63
Range	27–84	32–87	34–84	30–85	27–87
Sex (% of patients)					
Male	64	62	63	62	63
Female	36	38	37	38	37
Performance status (% of patients)†					
0	29	33	32	28	30
1	65	62	62	67	64
2	6	5	6	5	6
Brain metastases (% of patients)	12	14	13	12	13
Weight loss (% of patients)					
<5%	67	67	67	66	67
≥5%	33	33	33	34	33
Race or ethnic group (% of patients)					
White	87	84	87	83	85
Black	8	11	7	11	9
Other	5	5	6	6	6
Disease stage (% of patients)					
IIIB	11	14	14	14	13
IV or recurrent disease	89	86	86	86	87

*Reasons for ineligibility included incorrect stage (18 patients); histologic findings that were inconsistent with the diagnosis of non–small-cell lung cancer (7); prior chemotherapy (5); inadequate information on laboratory tests, radiographs, or performance status for documentation of eligibility (5); diagnosis of a second cancer (3); treatment that was not included in the protocol (3); coexisting conditions (3); poor performance status (3); progression of disease before treatment (2); withdrawal of consent (1), and other (2).

†A higher score indicates greater impairment.

nificant differences in response rates, survival, or the time to the progression of disease.

The overall response rate for the 1155 eligible patients was 19 percent (Table 3). In the group of patients who received cisplatin and paclitaxel, the median survival was 7.8 months, and the 1-year and 2-year survival rates were 31 percent and 10 percent, respectively (Table 3 and Fig. 2A). There were no significant differences in the response rate or survival among the three experimental-treatment groups. The median survival was 8.1 months among the patients who received cisplatin and gemcitabine, 7.4 months among those who received cisplatin and docetaxel, and 8.1 months among those who received carboplatin and paclitaxel (Table 3). The survival rate for those three groups was 36 percent, 31 percent, and 34 percent, respectively, at one year and 13 percent, 11 percent, and 11 percent, respectively, at two years.

The median time to the progression of disease was 3.4 months in the cisplatin-plus-paclitaxel group, as compared with 4.2 months in the cisplatin-plus-gemcitabine group (P=0.001 by the two-sided log-rank test) (Table 3). The median time to progression in the other two experimental-treatment groups did not differ significantly from that in the cisplatin-plus-paclitaxel group (Fig. 2B). Since the protocol specified that patients should be assessed for disease progression after every two cycles of treatment, patients who received cisplatin and docetaxel or carboplatin and paclitaxel, regimens that were administered in 21-day cycles, might have been found to have radiographic evidence of progression earlier than patients who received cisplatin and gemcitabine, which was administered in a 28-day cycle. However, that was not the case (data not shown).

According to the original trial design, patients with an ECOG performance status of 2, as well as those with a performance status of 0 or 1, were eligible for enrollment. However, in October 1997, after 66 patients with a performance status of 2 had

TABLE 2. OUTCOME FOR ALL TREATMENT GROUPS COMBINED.

VARIABLE	NO. OF PATIENTS	RESPONSE RATE	SURVIVAL			MEDIAN TIME TO PROGRESSION OF DISEASE
			MEDIAN	ONE YEAR	TWO YEARS	
		%	mo	%		mo
All patients	1207	19	8.0	34	12	3.7
Eligible patients	1155	19	7.9	33	11	3.6
Disease stage	1155					
IIIB		21	9.1	39	14	4.6
IV or recurrent disease		19	7.8	32	11	3.6
Sex	1155					
Male		19	7.4	30	10	3.5
Female		19	9.1	38	13	3.8
Performance status*	1155					
0		23	10.8†	42	16	4.3†
1		18	7.1	30	9	3.5
2		14	3.9	19	6	1.5

*A higher score indicates greater impairment.

†P<0.001 by the log-rank test for the comparison with a performance status of 1 or 2.

TABLE 3. OUTCOME ACCORDING TO TREATMENT GROUP.*

VARIABLE	CISPLATIN AND PACLITAXEL (N=288)	CISPLATIN AND GEMCITABINE (N=288)	CISPLATIN AND DOCETAXEL (N=289)	CARBOPLATIN AND PACLITAXEL (N=290)	TOTAL (N=1155)
Response — %					
Complete response	<1	1	<1	<1	<1
Partial response	21	21	17	16	19
Stable disease	18	18	25	23	21
Progressive disease	49	40	42	49	45
Could not be determined	13	20	16	11	15
Overall response rate — %	21	22	17	17	19
Survival					
Median (95% CI) — mo	7.8 (7.0–8.9)	8.1 (7.2–9.4)	7.4 (6.6–8.8)	8.1 (7.0–9.5)	7.9 (7.3–8.5)
1 yr (95% CI) — %	31 (26–36)	36 (31–42)	31 (26–36)	34 (29–40)	33 (30–36)
2 yr (95% CI) — %	10 (5–12)	13 (7–15)	11 (7–14)	11 (7–14)	11 (8–12)
Median time to progression (95% CI) — mo	3.4 (2.8–3.9)	4.2 (3.7–4.8)†	3.7 (2.9–4.2)	3.1 (2.8–3.9)	3.6 (3.3–3.9)

*Percentages may not sum to 100 because of rounding. CI denotes confidence interval.

†P=0.001 by the log-rank test for the comparison with cisplatin and paclitaxel.

been enrolled, the study design was amended to include only patients with a performance status of 0 or 1 because of the high rate of serious adverse events in the patients with a performance status of 2.[16] The median survival among patients with a performance status of 0 was 10.8 months, as compared with 7.1 months for patients with a performance status of 1 and 3.9 months for those with a performance status of 2 (P<0.001 by the log-rank test for both comparisons) (Table 2).

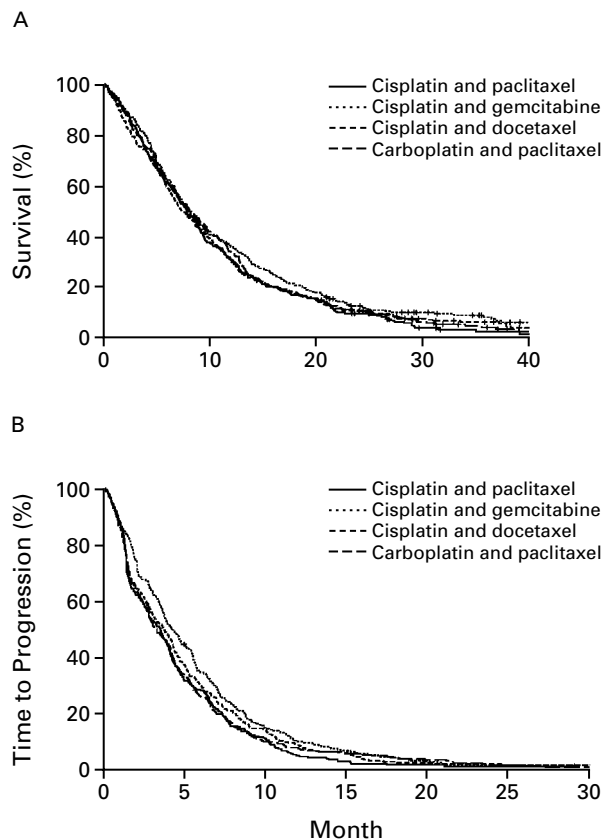Table 4 shows toxic complications in the four groups. These complications were the types usually

A

B

Figure 2. Kaplan–Meier Estimates of Overall Survival (Panel A) and the Time to Progression of Disease (Panel B) in the Study Patients, According to the Assigned Treatment.

associated with combination chemotherapy. They were similar in the four groups, with several exceptions, as noted in the table.

Fifty-three percent of the patients who received carboplatin and paclitaxel were withdrawn from the study because of progressive disease, as compared with 44 percent of the patients who received cisplatin and paclitaxel (P<0.001). Twenty-seven percent of the patients who received cisplatin and gemcitabine were withdrawn because of complications of therapy, as compared with 15 percent of the patients who received cisplatin and paclitaxel (P<0.001 by Fisher's exact test).

DISCUSSION

Cisplatin-based chemotherapy for metastatic non–small-cell lung cancer results in a small but statistically significant improvement in survival, as compared with supportive care alone.[2-4] Whereas older chemothera-

py regimens (e.g., mitomycin, ifosfamide, and cisplatin) resulted in survival rates of 10 to 15 percent at one year, second-generation regimens (e.g., cisplatin and etoposide) have typically resulted in survival rates of 20 to 25 percent at one year.[1,5,17-20] Our trial showed that third-generation regimens result in survival rates of 33 percent at one year and 11 percent at two years among patients with good performance status.

We sought to determine whether any of three newer third-generation chemotherapy regimens was superior to the first of these third-generation regimens, cisplatin plus paclitaxel, with respect to survival. There were no significant differences in survival between patients who received one of the three experimental regimens and those who received cisplatin and paclitaxel. Although the time to the progression of disease was longer in the group of patients who received cisplatin plus gemcitabine than in the other groups, this result was at the expense of greater renal toxicity. Given the lack of a survival benefit with this regimen and its greater toxicity, the clinical relevance of the increase in the time to disease progression is questionable.

Toxicity is particularly problematic in patients with a poor performance status. Patients with a performance status of 2 were excluded from our study after the early results suggested that such patients were likely to be more susceptible to adverse events, including death within 30 days from any cause, than were patients with a performance status of 0 or 1. Since the role of chemotherapy in the treatment of advanced non–small-cell lung cancer is supportive and palliative at best, the routine use of platinum-based combination chemotherapy in patients with a poor performance status cannot be recommended.

Although we did not obtain data on second-line chemotherapy in this study, it is possible that some of our patients crossed over to another therapy when the disease progressed. The effect of such a crossover on the results of this trial is unknown. We also did not compare the cost effectiveness of the four regimens, which is of potential importance, given the differences in the costs of the various drugs and in the costs associated with their administration.[21] Finally, the quality of life was not assessed in this study. Although reductions in toxicity are often assumed to improve the quality of life, in a recent Southwest Oncology Group study comparing cisplatin and vinorelbine with carboplatin and paclitaxel, there were no differences in the quality of life between the two treatment groups, despite significantly lower rates of toxic effects in the group of patients who received carboplatin and paclitaxel.[21]

We conclude that third-generation chemotherapy regimens in patients with non–small-cell lung cancer who have a good performance status can moderately

TABLE 4. TOXIC EFFECTS.*

TYPE OF TOXIC EFFECT	CISPLATIN AND PACLITAXEL (N=300)	CISPLATIN AND GEMCITABINE (N=293)	CISPLATIN AND DOCETAXEL (N=297)	CARBOPLATIN AND PACLITAXEL (N=293)
	% of patients			
Absolute neutrophil count				
Grade 3	18	24	21	20
Grade 4	57	39	48	43
Platelet count				
Grade 3	4	22	2	8
Grade 4	2	28†	1	2
Anemia				
Grade 3	12	27	13	9
Grade 4	1	1†	2	1
Infection				
Grade 3	4	4	5	3
Grade 4	4	2	2	2
Grade 5	2	1	2	1
Febrile neutropenia				
Grade 3	2	1	1	0
Grade 4	14	3†	10	4†
Cardiac toxic effects				
Grade 3	2	1	1	1
Grade 4	0	3	2	1
Grade 5	1	1	2	1
Renal toxic effects				
Grade 3	3	6	3	1
Grade 4	0	2	0	0
Grade 5	0	1†	0	0
Nausea				
Grade 3	25	37	24	9†
Vomiting				
Grade 3	3	7	3	2
Grade 4	21	28	18	6†
Diarrhea				
Grade 3	1	2	2	1
Grade 4	6	1	8	1
Hypersensitivity reactions				
Grade 3	2	0	5	1
Grade 4	1	0	2†	1
Weakness				
Grade 3	13	17	15	14
Grade 4	1	0	1	1
Neuropathy				
Grade 3	5	9	5	10
Highest grade (all toxic effects)				
3	19	21	23	28
4	68	68	61	53
5	5	4	6	4‡

*Data are for all patients who reported side effects, regardless of eligibility.

†P<0.05 for the sum of all grades shown, as compared with cisplatin and paclitaxel.

‡P<0.05 for the sum of grades 4 and 5, as compared with cisplatin and paclitaxel.

improve survival at one and two years. No significant difference in survival was observed among four commonly used regimens, although the regimen of carboplatin and paclitaxel had a lower rate of toxic effects than the other regimens. On the basis of these results, ECOG has chosen carboplatin and paclitaxel as its reference regimen for future studies.

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