Phase II Study of Paclitaxel and Epirubicin as First-Line Treatment in Patients with Metastatic Nonsmall Cell Lung Carcinoma

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BACKGROUND. The combination of paclitaxel and epirubicin has shown a favorable interaction in patients with advanced breast carcinoma. Therefore the efficacy and toxicity of this regimen was evaluated in a Phase II study of patients with metastatic nonsmall cell lung carcinoma (NSCLC).

METHODS. Thirty-two chemotherapy-naive patients with AJCC Stage IV NSCLC and an Eastern Cooperative Oncology Group performance status of 0–1 were entered into the study. Patients received epirubicin, 90 mg/m^2, followed by paclitaxel, 175 mg/m^2 by 3-hour infusion, on Day 1. The treatment was repeated every 3 weeks. Granulocyte-colony stimulating factor (G-CSF) was not used routinely.

RESULTS. A total of 116 treatment cycles was delivered. All patients could be assessed for response, toxicity, and survival. There were 16 partial responses and no complete responses, giving rise to an overall response rate of 50% (95% confidence interval, 31.9–68.1%). The median time to progression in responders was 7 months. The median survival was 8 months, and the 1-year survival rate was 37%. World Health Organization Grade 4 neutropenia occurred in 69% of patients, but could be managed easily with G-CSF, which was used in 35% of cycles. Cumulative peripheral neuropathy was the main nonhematologic toxicity and was observed in 7 of 8 patients who received 6 treatment courses (Grade 2–3 in 3 cases) and in 6 of 11 patients who received 4 cycles (Grade 2 in 2 patients). One patient died shortly after the first course of chemotherapy from a ventricular arrhythmia.

CONCLUSIONS. The combination of paclitaxel and epirubicin was found to be effective and well tolerated in chemotherapy-naive patients with metastatic NSCLC and warrants further evaluation in a multicenter trial of a larger number of patients. Careful cardiac evaluation before treatment is indicated. ***Cancer* 2000;89: 89–96.** *© 2000 American Cancer Society.*

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After many years of debate regarding the role of chemotherapy in advanced nonsmall cell lung carcinoma (NSCLC),[1] several randomized trials comparing best supportive care versus chemotherapy[2] and meta-analyses of these trials[3] have demonstrated a small, short term, but significant survival benefit in favor of cisplatin-containing combination chemotherapy. Based upon this observation, therefore, platinum-based combination chemotherapy is considered as a reasonable standard of care for selected patients with advanced NSCLC.[4]

However, the survival improvement is modest, and platinum-based regimens have considerable toxicity. The recent introduction of new active agents such as paclitaxel, docetaxel, irinotecan, topotecan, and gemcitabine[5,6] has increased the possibility of developing effective and less toxic combinations. Single-agent paclitaxel has produced

response rates exceeding 20% and 1-year survival in the range of 40% using different schedules.[7,8] In the past few years, paclitaxel has been combined with different agents, which were considered to be active in NSCLC. In particular, paclitaxel was safely combined with both cisplatin and carboplatin[9–14]; these regimens were successfully compared in randomized studies with combinations that have been hitherto considered standard treatment in advanced NSCLC.[15–17] Moreover, paclitaxel has been tested with agents other than platinum compounds. The taxanes have shown favorable interaction with anthracyclines in preclinical and clinical studies in other malignancies such as breast carcinoma.[18]

Epirubicin is the 4′ epimer of doxorubicin and has been used alone or in combination with other cytotoxic agents in the treatment of a variety of tumors. It has both a lower myelotoxicity and a lower propensity to produce cardiotoxic effects than doxorubicin.[19] Several studies have evaluated the efficacy of epirubicin alone for treatment of advanced NSCLC; single-agent therapy with standard doses ($\leq$ 90 mg/m^2) produced discouraging results,[20] whereas activity was more significant using higher doses ($\geq$ 120 mg/m^2), with response rates of approximately 20%.[21]

Even if epirubicin cannot be considered as a reference agent in the treatment of patients with NSCLC, the high activity and the favorable toxicity profile when combined with paclitaxel for the treatment of advanced breast carcinoma [18,22] prompted us to explore the activity and the toxicity of this regimen in chemotherapy-naive patients with Stage IV NSCLC in a Phase II trial.

MATERIALS AND METHODS

Eligibility

The single-institutional Phase II trial was initiated in August 1997. Chemotherapy-naive patients with histologically or cytologically proven metastatic NSCLC and bidimensionally measurable disease were entered into the study. Patients with recurrent metastatic disease after surgery were eligible for the study; prior radiotherapy, either in the adjuvant setting or for the treatment of metastatic lesions, was allowed, provided that the patient had measurable disease outside the radiation field. Patients with brain metastases could be enrolled only if they were neurologically asymptomatic and had another measurable site of disease.

Patients were eligible if they were between 18 and 70 years of age and had a performance status (PS) of 0–1 on the Eastern Cooperative Oncology Group (ECOG) scale. Patients were required to have normal renal (creatinine concentration $<$ 1.5 mg/dL) and hepatic function (bilirubin concentration $<$ 1.5 mg/dL, aspartate aminotransferase $\leq$ 2 times the upper limit of the laboratory normal range). Additional eligibility requirements included the following hematologic parameters: white blood cells $\geq$ 4000/μL (with an absolute granulocyte count $>$ 2000/μL), hemoglobin level $\geq$ 11 g/L, and platelet count $>$ 100,000/μL . Patients with a history of acute myocardial infarction within the last 6 months or with arrhythmias or chronic heart failure requiring permanent medication were excluded from the study. Patients treated for any other type of cancer during the previous 5 years and patients with serious coexisting medical illnesses also were excluded. A negative pregnancy test was required for women of childbearing potential. All patients gave informed consent before beginning treatment.

Treatment Plan

All patients received the following chemotherapy regimen: epirubicin 90 mg/m^2 administered by intravenous (i.v.) bolus immediately before the infusion of paclitaxel 175 mg/m^2 over 3 hours. The premedication schedule consisted of dexamethasone 20 mg i.v. 30 minutes before paclitaxel infusion, intramuscular orphenadrine 40 mg, and intravenous ranitidine 100 mg 1 hour before the start of treatment. Patients received intravenous prophylactic antiemetic therapy with a 5-HT^3 antagonist before treatment, which was continued orally for 48 hours. Chemotherapy was administered in the outpatient setting every 3 weeks. Initially a maximum of 6 courses was planned; however, after the first 15 patients, this regimen was terminated and changed to a maximum of 4 courses. This alteration was due to the occurrence of one case of severe peripheral neuropathy after 6 cycles (see "Results").

No standard dose modification was planned. Use of granulocyte colony-stimulating factor (G-CSF) was allowed to treat Grade 4 neutropenia in selected patients with high risk of infection (febrile neutropenia, previous irradiation to areas containing large amounts of bone marrow, documented occurrence of prolonged neutropenia in an earlier cycle). A short duration of administration was adopted, withdrawing G-CSF treatment when a clinically adequate neutrophil recovery was achieved ($\geq$ 1000/μL).

Evaluations

Baseline evaluations included patient medical history, physical examination, complete blood cell (CBC) count with differential and platelet count, liver and kidney function tests, electrocardiogram (ECG), computed tomography (CT) scans of the chest, abdomen, and brain, and whole bone scan.

During treatment, CBCs with differential and platelet count were performed weekly, whereas bio-

chemical tests and physical examination were repeated every 3 weeks.

All patients who completed two cycles of chemotherapy were evaluated for response, according to World Health Organization (WHO) criteria.[23] A complete response (CR) was defined as the disappearance of all lesions for at least 4 weeks; a partial response (PR) required a $\geq$ 50% decrease in the tumor size (the sum of the products of the largest perpendicular diameters of all measurable lesions); stable disease (SD) was defined as $<$ 50% decrease or $<$ 25% increase in tumor size. Progressive disease (PD) was defined as an increase of at least 25% in tumor size or the appearance of new lesions. Patients with a rapid objective progression after one cycle were considered PD. All patients who received at least one course of treatment were included in the analysis of treatment-related toxicities, which were recorded according to WHO criteria.[23] Dose intensity (DI) for each drug was calculated according to the method proposed by Longo et al.[24]

After restaging, further treatment was planned depending on response and toxicity. Therapy was discontinued if PD was observed. Patients with SD or an objective response continued treatment, with reassessment after every two cycles of chemotherapy. All patients registered on the study were evaluated in the survival analysis.

Statistical Methods

Confidence limits (95% confidence interval [CI]) of response rate were estimated.[25] Time to progression (TTP) was defined as the period from the first day of treatment to the date of first evidence of disease progression; survival was calculated from the first day of therapy until death or last follow-up. Actuarial survival curves were generated using the method of Kaplan and Meier.[26]

RESULTS

Patient Characteristics

Between August 1997 and May 1999, a total of 32 patients entered the study. All patients were chemotherapy-naive, had Stage IV NSCLC, and could be assessed for response, toxicity, and survival. The characteristics of the 32 patients are summarized in Table 1. There were 28 males and 4 females, with a median age of 58 years. All the patients had a good PS (0–1 according to ECOG scale). The majority had adenocarcinoma histologic subtype (62%). Six patients had been treated previously with surgery, one case followed by adjuvant radiotherapy on the mediastinum. At the time of the study entry, 17 patients had 2 or more metastatic sites, whereas 15 had 1 metastatic site only. In particular, 50% had metastatic lung involvement, 47% bone involvement, and 12% liver involvement. Pleural metastases were present in 19%, whereas 9% of patients had adrenal gland involvement. Three patients (9%) had asymptomatic brain metastases, detected during baseline staging by brain CT scan. These patients entered the study protocol and were treated concomitantly on central nervous system disease with whole brain radiation (one case) and stereotactic radiosurgery (two cases); for these patients, response was evaluated on other sites of measurable disease outside the brain.

TABLE 1
Patient Characteristics (n = 32)

Characteristic	No.	%
Gender male/female	28/4	
Age (yrs)		
Median	58	
Range	37–70	
ECOG performance status		
0	15	47
1	17	53
Weight loss (%)		
$<$ 5%	22	69
$\geq$ 5%	10	31
Histology		
Adenocarcinoma	20	63
Squamous cell carcinoma	8	25
Large cell carcinoma	2	6
Undifferentiated NSCLC	2	6
Prior therapy		
Yes (surgery/RT)	6	19
No	26	81
Organ involvement		
1 metastatic site	15	47
$\geq$ 2 metastatic sites	17	53

ECOG: Eastern Cooperative Oncology Group; NSCLC: nonsmall cell lung carcinoma; RT: radiotherapy.

Efficacy

All of the 32 patients could be evaluated for response, which was documented with CT scans. Twenty-six of 32 patients received at least 2 courses and were evaluated for response after the second cycle; an additional 5 patients received only 1 course of treatment due to rapid progression of disease and were categorized as nonresponders. One patient died suddenly on Day 5 after the first cycle for a ventricular arrhythmia and also was categorized as a nonresponder. A PR was achieved in 16 patients, whereas no CR was registered; the objective response rate was 50% (95% CI, 31.9–68.1%). Four patients (12.5%) had SD after two courses of chemotherapy, and 12 (37.5%) had PD.

Median TTP in responders was 7 months (range, 2–20 months); 4 responders were free from progres-

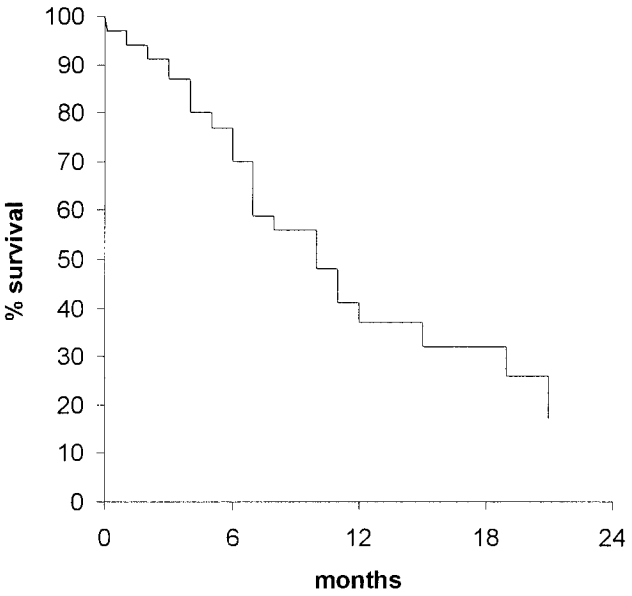

FIGURE 1. Kaplan–Meier estimation of actuarial overall survival for the 32 patients is shown. One-year survival was 37%.

sion at a median follow-up of 13 months. Median TTP in patients with SD was 4.5 months (range, 3–5 months). Median TTP for the 11 patients receiving 4 cycles was 6 months versus 7 months for patients treated with 6 cycles of chemotherapy. Figure 1 shows the actuarial survival curve for the entire population; median survival was 8 months (range, 0–23 months); 1-year survival was 37%. Overall, at median follow-up of 12 months for living patients, 11 patients were alive, 4 without any evidence of disease progression.

Dose Analysis

A total of 116 treatment cycles was delivered, with a median of 4 per patient (range, 1–6 cycles). A maximum of 6 courses was planned for the first 15 patients; however, only 8 patients received the whole treatment. Among these patients, a further regression in tumor burden between the fourth and the sixth cycle was observed in only 2 cases; however, 7 of these patients developed a peripheral neuropathy, of Grade 2–3 in 3 cases. For this reason, we modified the treatment protocol and withdrew the treatment even for responders after a maximum of four courses. No patient refused to continue chemotherapy for reasons directly related to the treatment toxicity. Therapy was discontinued only if disease progression was observed or at the completion of the planned number of cycles. A dose reduction was required in only 2 cases, 1 due to persistent neutropenia and 1 to Grade 2 hepatotoxicity. Because of dose reductions and treatment delays, the median delivered DI was 54 mg/m^2/week for paclitaxel (range, 37–61) and 28 mg/m^2/week for epirubicin (range, 19-31), representing 93% of the planned DI (58 mg/m^2/week for paclitaxel and 30 mg/m^2/week for epirubicin).

TABLE 2
Hematological Toxicity by Patient

	WHO toxicity grade			
Condition	**1 (%)**	**2 (%)**	**3 (%)**	**4 (%)**
Neutropenia	—	2 (6)	3 (9)	22 (69)
Thrombocytopenia	2 (6)	1 (3)	—	—
Anemia	7 (22)	6 (19)	2 (6)	—

WHO: World Health Organization.

TABLE 3
Nonhematological Toxicity by Patient

	WHO toxicity grade			
Condition	**1 (%)**	**2**	**3**	**4**
Arthralgia/myalgia	10 (31)	3 (9)	—	—
Peripheral neuropathy	10 (31)	6 (19)	1 (3)	—
Skin toxicity	1 (3)	—	—	—
Nausea/emesis	9 (28)	4 (12)	—	—
Diarrhea	—	2 (6)	—	—

WHO: World Health Organization.

Toxicity

The treatment was well tolerated by most patients. Myelosuppression was the main toxicity (Table 2), with Grade 3–4 neutropenia witnessed in 25 patients (78% of the whole study group). G-CSF was administered to 16 of 26 patients who received 2 or more courses of chemotherapy (62%). Actually, the G-CSF was administered in 41 cycles only (35% of all courses); in approximately half of the patients who received growth factor support, it was used once only. In most cases, it was not administered after the first cycle, but late in the course of treatment. Median duration of G-CSF schedule was 3 days. All the patients were treated on a outpatient basis; only one patient was hospitalized for septic fever, which was stopped with antibiotic therapy and G-CSF support. Anemia and thrombocytopenia were less common. Two patients with Grade 3 anemia required packed red blood cell transfusions. Nonhematologic toxicity is summarized in Table 3. Nausea and vomiting were mild and were easily controlled with antiemetics. The arthralgia/myalgia syndrome was common, but no severe case was observed. Peripheral neuropathy was more frequent

and generally developed after the third or fourth course of chemotherapy. In particular, neurotoxicity was observed in 7 of 8 patients who received 6 treatment courses (Grade 2–3 in 3 cases), and in 6 of 11 patients who received 4 cycles (Grade 2 in 2 patients). Only one patient had a mild skin reaction, which did not require withdrawal from therapy. One patient died on Day 5 of the first course of chemotherapy with acute dyspnoea and thoracic pain: no hematologic toxicity was found; liver and kidney function tests were normal; ECG revealed a ventricular arrhythmia. No previous cardiac disease was known, and autopsy was not performed. Two cases of pulmonary embolism were observed (one asymptomatic, detected at CT scan evaluation), along with a case of deep venous thrombosis of the left arm; all these patients recovered with anticoagulant therapy.

DISCUSSION

Between 40% and 50% of patients with NSCLC present with metastatic disease, whereas local disease for 75% of the patients ultimately will recur in distant sites.[1] The optimal management of these patients is controversial, but there is general agreement[4] that cisplatin-based chemotherapy, when compared with best supportive care alone, improves survival[3] and quality of life[27] and reduces symptoms. However, the survival benefit is small, with an increased median survival of 6 weeks and the 1-year survival rate improved by only 10% (from 15% to 25%).[3] Furthermore, efficacy of cisplatin-based programs is such that no specific regimen can be regarded as standard therapy.[28] Unfortunately, in spite of improvement of supportive care, these regimens still have considerable toxicity, including emesis, peripheral neuropathy, and nephrotoxicity and hearing loss. These modest results have made the development of new agents and combinations imperative.

Recently, several new drugs have been shown to be active for advanced NSCLC, with approximately a 20% response rate for single agents and a favorable toxicity profile.[5] In particular, reports of paclitaxel combinations have shown relatively high response rates, significant 1-year survival and palliation of cancer symptoms.[5,6] Dual drug combinations with both cisplatin and carboplatin are the most extensively studied,[5,6,29] and triplet chemotherapy regimens based on platinum–paclitaxel combination with the addition of another new agent are under development.[30] However, paclitaxel has only been tested in a few trials in combination with nonplatinum compounds.[31–34]

The current article reports the results of one of the first Phase II trials to our knowledge describing the use of the combination of paclitaxel and epirubicin in chemotherapy-naive patients with metastatic NSCLC. The study was planned on the basis of the high activity and the favorable toxicity profile of the combination of anthracyclines and paclitaxel for the treatment of advanced breast carcinoma.[18,22] Preclinical studies in breast carcinoma have reported conflicting data, with some studies showing subcumulative cytotoxicity and others sequence-dependent synergy. A schedule-dependent interaction has been demonstrated in pharmacokinetic studies, with doxorubicin clearance reduced in the sequence paclitaxel–doxorubicin as compared with doxorubicin-paclitaxel. However, the pharmacokinetic interferences of anthracycline–paclitaxel are different according to the anthracycline used.[18]

The regimen used in this study was modeled on the maximum-tolerated dose obtained in a dose-finding study in advanced breast carcinoma.[22] The dose of paclitaxel was reduced from 200 mg/m^2 to 175 mg/m^2 to partially alleviate the development of neuropathy in NSCLC patients, who have theoretically major risk factors (smoking, chronic alcohol abuse) than women with breast carcinoma. To improve the reliability of results, we elected to use more restricted eligibility criteria, excluding Stage IIIB patients, who are more likely to respond to chemotherapy than those with Stage IV disease.[35] However, we only enrolled patients with ECOG PS 0–1, who have a higher probability of achieving a survival benefit and are less likely to experience severe treatment-related toxicity.[35] Weight loss, another definite predictor in advanced NSCLC,[35] was not considered for patient selection in our trial; a weight loss $\geq$ 5% was present in a third of the cases. In our study population, the combination of paclitaxel and epirubicin proved effective, with an overall response rate of 50% (95% CI, 31.9–68.1 %). Median duration of response (i.e., TTP in responders) was 7 months. Median survival was 8 months, with 1-year survival rate of 37%. These data confirmed the results of two other small studies evaluating the combination of paclitaxel and anthracyclines in advanced NSCLC[36,37] (Table 4).

The survival rate of our series is similar to those obtained with single-agent paclitaxel and with the more widely used paclitaxel–platinum combinations.[7–17] However, survival is not a correct endpoint for Phase II trials evaluating new agents or new combinations in advanced NSCLC. Patient populations enrolled in these studies can vary a lot: in particular, some trials have few Stage IV patients, whereas others, including our study, are restricted to metastatic disease. Only comparative trials can answer the question

TABLE 4
Paclitaxel and Anthracyclines in Advanced NSCLC

Author	Regimen (mg/m^2)[a]	No. patients	Stage IV (%)	RR (%)	Median Sv	1-yr Survival (%)
Greenberg et al.[36]	DOX 50 mg/m^2 i.v. bolus, Day 1 TAX 135 mg/m^2 i.v. 24 hrs, Day 1	12	100	33	nr	nr
Chen et al.[37]	DOX 40 mg/m^2 i.v. bolus, Day 1 TAX 150 mg/m^2 i.v. 3 hrs, Day 2	15	74	53	35 wks	33
Chen et al.[37]	EPI 70 mg/m^2 i.v. bolus, Day 1 TAX 175 mg/m^2 i.v. 3 hrs, Day 2	27	100	52	nr	nr
Current study	EPI 90 mg/m^2 i.v. bolus, Day 1 TAX 175 mg/m^2 i.v. 3 hrs, Day 1	32	100	50	8 mos	36

[a] All regimens were administered every 3 weeks. Only chemotherapy-naive patients assessable for response were considered. G-CSF was routinely given in all cases except for the current study.
NSCLC: nonsmall cell lung carcinoma; RR: response rate; DOX: doxorubicin; TAX: paclitaxel; nr: not reported; EPI: epirubicin.

if higher response rates are consistently associated with improvement in survival.

Myelosuppression was the main toxicity observed, with 78% of patients developing Grade 3–4 neutropenia at least once during the treatment; however, only 1 patient was hospitalized for a septic fever requiring intensive support. For all the other patients, the hematologic toxicity was quickly reverted, in 41 cycles (35% of all courses) with the use of G-CSF support. G-CSF was administered in selected cases only, when an high risk of infection was predictable, and for a short duration, stopping G-CSF treatment when a clinically adequate neutrophil recovery was achieved. All the patients were treated on a outpatient setting, and this could have increased the risk of complications in case of profound and prolonged neutropenia. Even if no cost-effectiveness analysis was considered, the minimal need for hospitalization and parenteral antibiotics in the current trial could justify the increase of expense due to a selective use of growth factors for this regimen.

The fatal ventricular arrhythmia that occurred in one of our patients a few days after the first course of chemotherapy probably should be attributed to the treatment regimen, even if acute cardiotoxicity with clinically significant events rarely has been described for both epirubicin and paclitaxel.[38,39] Cardiotoxicity of anthracyclines is usually dose-dependent and is enhanced by the pharmacokinetic interactions with taxanes.[18] These interactions are schedule-dependent, with the sequence paclitaxel–anthracyclines more toxic as compared with the opposite sequence.[40] Epirubicin is less cardiotoxic than doxorubicin[19] and its combination with paclitaxel does not show the potentiation of cardiac toxic effects that is observed with doxorubicin.[22] No other cases of cardiac side effects were observed in our series; however, a thorough baseline cardiac evaluation is advisable in NSCLC patients submitted to this regimen.

Because neutropenia can be managed easily by the administration of G-CSF, peripheral neuropathy has become the main dose-limiting toxicity in paclitaxel-based chemotherapy.[41] Its severity increases with increasing single and cumulative drug doses[42] and is accentuated by short infusions[14] and in regimens also containing a platinum analog.[42] Cumulative peripheral neuropathy of Grade 3 occurred in only 1 patient in our series, whereas Grade 2 was observed in 6 cases (19%). These data compare favorably with the higher percentages of severe neurotoxicity reported in some trials using the combination of paclitaxel with carboplatin[14] and in most of the studies with cisplatin–paclitaxel regimens.[15,41]

The issue of duration of chemotherapy administration in Stage IV NSCLC is controversial. Given the palliative objective of therapy in these patients, the duration of treatment should be balanced against the toxicity it engenders.[4] Few studies have addressed this point. A recent randomized trial that used a cisplatin-based regimen showed no difference in survival between three and six courses of chemotherapy, with substantially enhanced toxicity for long term treatment.[43] Although the numbers are small, in the current study TTP for patients receiving either four or six cycles of therapy was very similar, despite a higher incidence of neurotoxicity in patients treated with six cycles. In our opinion, short term treatment should be compared with standard duration therapy (six to eight cycles) even with the new paclitaxel-based regimens.

In conclusion, the combination of paclitaxel and epirubicin administered for 4 courses is active against metastatic NSCLC, with encouraging 1-year survival and limited toxic effects. Neutropenia is easily manageable with selective use of G-CSF in high risk cases. Careful cardiac evaluation of patients before treatment is indicated. Even if comparisons are difficult out of the context of Phase III trials, our study supports a possible role for modern nonplatinum regi-

mens in first-line treatment of metastatic NSCLC.[44] A multicenter Phase II trial on a larger number of patients, with extramural independent response review, is currently ongoing to confirm our promising data.

REFERENCES

1. Ihde DC. Chemotherapy of lung cancer. *N Engl J Med* 1992; 12:1434–41.
2. Rapp E, Pater JL, Willan A, Carmier Y, Murray N, Evans WK, et al. Chemotherapy can prolong survival in patients with advanced non-small cell lung cancer: report of a Canadian multi-center randomized trial. *J Clin Oncol* 1988;6:633–41.
3. 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. *Br Med J* 1995;311:899–909.
4. American Society of Clinical Oncology. Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. *J Clin Oncol* 1997;15:2996–3018.
5. Bunn PA, 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;5:1087–100.
6. Shepherd FA. Chemotherapy for non-small cell lung cancer: have we reached a new plateau? *Semin Oncol* 1999;1(Suppl 4):3–11.
7. Chang AI, Kim K, Glick J, Anderson T, Karp D, Johnson D. Phase II study of Taxol, Merbarone, and Piroxantrone in stage IV non-small-cell lung cancer: the Eastern Cooperative Oncology Group results. *J Natl Cancer Inst* 1993;85:388–94.
8. Murphy WK, Fossella FW, Winn RJ, Shin DM, Hynes HE, Gross HM, et al. Phase II study of Taxol in patients with untreated advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1993;85:384–8.
9. Rowinsky E, Chaudhry V, Forastierre AA, Sartorius SE, Ettinger DS, Grochow LB, et al. Phase I and pharmacologic study of paclitaxel and cisplatin with granulocyte colony stimulating factors: neuromuscular toxicity is dose-limiting. *J Clin Oncol* 1993;11:2010–20.
10. Klastersky J, Sculier JP. Dose finding study of paclitaxel (Taxol) plus cisplatin in patients with non-small cell lung cancer. *Lung Cancer* 1995;12(2 Suppl):117–25.
11. Von Pawel J, Wagner H, Niederle N, Heider A, Koschel G, Gromotka E, et al. Phase II study of paclitaxel and cisplatin in patients with non-small cell lung cancer. *Semin Oncol* 1996;23(16 Suppl):47–50.
12. Langer CJ, Leighton JC, Comis RL, O'Dwyer PJ, McAleer CA, Bonjo CA, et al. Paclitaxel and carboplatin in combination in the treatment of advanced non-small cell lung cancer: a phase II toxicity, response and survival analysis. *J Clin Oncol* 1995;13:1360–70.
13. Johnson DH, Paul DM, Hande KR, Shyr Y, Blanke C, Murphy B, et al. Paclitaxel plus carboplatin in advanced non-small-cell lung cancer: a phase II trial. *J Clin Oncol* 1996;14:2054–60.
14. Hainsworth JD, Urba WJ, Hon JK, Thompson KA, Stagg MP, Hopkins LG, et al. One-hour paclitaxel plus carboplatin in the treatment of advanced non-small cell lung cancer: results of a multicentre, phase II trial. *Eur J Cancer* 1997;34: 654–8.
15. Giaccone G, Splinter TAW, Debruyne C, Khot GS, Lianes P, van Zandwijk N, 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.
16. Bonomi P, Kim K, Chang A, Johnson D. Phase III trial comparing etoposide cisplatin versus taxol with cisplatin-G-CSF versus taxol-cisplatin in advanced non-small cell lung cancer. An Eastern Cooperative Oncology Group (ECOG) trial. *Proc Am Soc Clin Oncol* 1996;15:382.
17. Kelly K, Crowley J, Bunn PA, Livingston RB, Gandara DR. A randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in untreated advanced non-small cell lung cancer: a Southwest Oncology Group (SWOG) trial. *Proc Am Soc Clin Oncol* 1999;18:461a.
18. Conte PF, Gennari A. Anthracyclines-paclitaxel combinations in the treatment of breast cancer. *Ann Oncol* 1997;8: 939–43.
19. Plosker GL, Faulds D. Epirubicin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cancer chemotherapy. *Drugs* 1993;45:788–856.
20. Kalman LA, Kris MG, Gralla RJ, Kelsen DP. Phase II trial of 4′ epi-doxorubicin in patients with non-small cell lung cancer. *Cancer Treat Rep* 1983;67:591–2.
21. Feld R, Wierzbicki R, Walde PLD, Sheperd FA, Evans WK, Gupta S, et al. Phase I-II study of high-dose epirubicin in advanced non-small cell lung cancer. *J Clin Oncol* 1992;10: 297–303.
22. Conte PF, Baldini E, Gennari A, Michelotti A, Salvadori B, Tibaldi C, et al. Dose-finding study and pharmacokinetics of epirubicin and paclitaxel over 3 hours: a regimen with high activity and low cardiotoxicity in advanced breast cancer. *J Clin Oncol* 1997;15:2510–7.
23. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–14.
24. Longo DL, Duffey PL, De Vita VT, Wesley MN, Hubbard SM, Young RC. The calculation of actual or received dose intensity: a comparison of published methods. *J Clin Oncol* 1991; 9:2042–51.
25. Simon R. Confidence intervals for reporting results of clinical trials. *Ann Intern Med* 1986;105:429–35.
26. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
27. Billingham LJ, Cullen MH, Woods J, Chettiyawardana AD, Joshi RC, Cook J, et al. Mitomycin, ifosfamide and cisplatin (MIC) in non-small cell lung cancer: results of a randomised trial evaluating palliation and quality of life. *Lung Cancer* 1997;18(1 Suppl):9–10.
28. Weick JK, Crowley J, Natale RB, Hom BL, Rivkin S, Coltman CA Jr., et al. A randomized trial of five cisplatin-containing treatments in patients with metastatic non-small-cell lung cancer: a Southwest Oncology Group study. *J Clin Oncol* 1991;9:1157–62.
29. Bonomi P. Review of paclitaxel/carboplatin in advanced non-small cell lung cancer. *Semin Oncol* 1999;26(2 Suppl): 55–9.
30. Bunn PA. Triplet chemotherapy with gemcitabine, a platinum, and a third agent in the treatment of advanced non-small cell lung cancer. *Semin Oncol* 1999;26(4 Suppl):25–30.
31. Shepherd FA, Latreille J, Crump M, Stewart D, Tomiak E, Eisenhauer E, et al. Phase I trial of paclitaxel (Taxol) and ifosfamide in previously untreated patients with non-small cell lung cancer. *Ann Oncol* 1996;7:311–3.
32. Rosell R, Felip E, Massuti B, Gonzalez-Larriba JL, Benito D, Lopez-Cabrerizo MP, et al. A sequence-dependent paclitaxel/etoposide Phase II trial in patients with non-small cell lung cancer. *Semin Oncol* 1997;24(12 Suppl):56–60.

33. Chang A, De Vore R, Johnson DL. Pilot study of vinorelbine (Navelbine) and paclitaxel in patients with refractory non-small cell lung cancer. *Semin Oncol* 1996;23(5 Suppl):19–21.
34. Georgoulias V, Kourousis C, Kakolyris S, Androulakis N, Dimopoulos MA, Papadakis E, et al. Second-line treatment of advanced non-small cell lung cancer with paclitaxel and gemcitabine: a preliminary report on an active regimen. *Semin Oncol* 1997;24(12 Suppl):61–6.
35. Paesmans M, Sculier JP, Libert P, Bureau J, Dabouis G, Thiriaux J, et al. Prognostic factors for survival in advanced non-small cell lung cancer: univariate and multivariate analysis including recursive partitioning and amalgamation algorithms in 1052 patients. *J Clin Oncol* 1995;13:1221–30.
36. Greenberg R, Friedland D, Holroyde C, Terzian A, Lerner W, Gorman G, et al. Phase II trial of taxol and adriamycin in stage IV non-small cell lung carcinoma. *Proc Am Soc Oncol* 1995;14:374.
37. Chen MC, Chiang AA, Chow JM, Yeh KH, Wang CC, Yang CH, et al. Paclitaxel in combination with doxorubicin or epirubicin in treating advanced non-small-cell lung cancer. *Proc Am Soc Oncol* 1998;17:480a.
38. Rowinsky EK, McGuire WP, Guarnieri T, Fisherman JS, Christian MC, Donehower RC. Cardiac disturbances during administration of taxol. *J Clin Oncol* 1991;9:1704–12.
39. Grenier MA, Lipshultz SE. Epidemiology of anthracycline cardiotoxicity in children and adults. *Semin Oncol* 1998; 25(10 Suppl):72–85.
40. Gianni L, Munzone E, Capri G, Fulfaro F, Tarenzi E, Villani F, et al. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J Clin Oncol* 1995;13:2688–99.
41. Berger T, Malayeri R, Doppelbauer A, Krajnik G, Huber H, Auff E, et al. Neurological monitoring of neurotoxicity induced by paclitaxel/cisplatin chemotherapy. *Eur J Cancer* 1997;33:1393–9.
42. Von Gerven JMA, Moll JWB, Van den Bent MJ, Bontenbal M, van der Burg ME, Verweij J, et al. Paclitaxel (Taxol) induces cumulative mild neurotoxicity. *Eur J Cancer* 1994;30:1074–7.
43. Smith IE, O'Brien MER, Norton A, Ashley S, Webb A, Nicolson M, et al. Duration of chemotherapy for advanced non-small cell lung cancer: a phase III randomised trial of 3 versus 6 courses of mitomycin C, vinblastine, cisplatin (MPV). *Proc Am Soc Oncol* 1998;17:457a.
44. Ruckdeschel JC, Gridelli C, Perrone F, Monfardini S, Giaccone G. Are platinum compounds mandatory in the treatment of metastatic non-small cell lung cancer? *Eur J Cancer* 1998;34:1993–9.