Cancer Chemother Pharmacol (1990) 26: 52–56

Cancer Chemotherapy and Pharmacology

A randomized trial of three cisplatin-containing regimens in advanced non-small-cell lung cancer (NSCLC): a study of the Umbrian Lung Cancer Group*

Lucio Crino[1], Maurizio Tonato[1], Samir Darwish[1], Maria L. Meacci[1], Enrichetta Corgna[1], Francesco Di Costanzo[2], Franco Buzzi[2], Giovanni Fornari[3], Emilio Santi[3], Enzo Ballatori[5], Carla Santucci[5], and Stephen Davis[6], **

Divisions of [1] Medical Oncology, [3] Medicine and Pneumology, Policlinico Hospital, Perugia, Italy; [2] Oncology Service, Terni, Italy; [5] Departments of Statistics and [6] Internal Medicine, University of Perugia, Italy

Received 31 March 1989/Accepted 12 July 1989

Summary. Survival in patients with locally advanced (stage III Mo) and metastatic (M1) non-small-cell lung cancer (NSCLC) is short. Phase II studies have reported objective responses ranging from 20% to 60% using cisplatin-based chemotherapeutic regimens, yet few have shown improvement in median survival. In our phase II pilot studies with cisplatin (CDDP) and etoposide (VP-16), we observed a 26% response rate; with CDDP, VP-16, and mitomycin-C, a 38% response rate was obtained in advanced NSCLC patients. A total of 156 consecutive patients with locally advanced and metastatic NSCLC were randomized to one of three treatment arms to determine whether the chemotherapy protocols had any effect on response rate and median survival in a large, randomized study. Arm 1 consisted of CDDP (120 mg/m^2 × 3 weeks); arm 2, of CDDP (120 mg/m^2) and VP-16 (100 mg/m^2 given i.v. on days 1–3), repeated every 3 weeks; and arm 3, of CDDP (120 mg/m^2) and VP-16 (100 mg/m^2 on days 1–3) given every 3 weeks, plus mitomycin C (10 mg/m^2 on days 1, 21, and 42, then every 6 weeks, for a maximal dose of 100 mg). After 71 patients had been enrolled in the study, we stopped accrual in the CDDP arm due to a lack of response [1 complete response (CR) in 24 patients; 4%] and continued enrollment in the two combination-chemotherapy arms. In the CDDP/VP-16 arm a 30% response rate [1 CR, 18 partial responses (PRs)] was obtained, and in the CDDP/VP-16 mitomycin C arm a 26% response rate (4 CRs, 11 PRs) was seen among a total of 150 evaluable patients. Responses were observed in 31% of patients with favorable performance status (PS) (ECOG 0–1) vs 14% in patients with a poor PS (ECOG 2–3). Of patients with locally advanced disease (III Mo), 17 (33%) obtained an objective response, compared with 20 patients (20%) with metastatic disease. Median survival was 18 weeks in the CDDP arm, 35 weeks in the CDDP/VP-16 arm, and 37 weeks in the CDDP/VP-16/mitomycin C arm. The median survival in the multimodal chemotherapy arms was significantly greater than that obtained with CDDP alone. Toxicity was predominantly myelosuppression in the mitomycin C-containing arm (27%, wtto grade 3–4). Our study shows that combination chemotherapy using CDDP/VP-16 is active and safe in the treatment of advanced NSCLC patients with a good performance status. The addition of mitomycin C did not improve the therapeutic response.

Introduction

Lung cancer is the leading cause of cancer deaths in the Western world. Surgical resection is the only effective curative treatment for patients with non-small-cell lung cancer (NSCLC), but >75% of patients have inoperable disease at the time of diagnosis. The prognosis is dismal; median survival for untreated patients with inoperable limited disease is 36 weeks, and that for patients with extensive disease, 14 weeks [11].

Combination chemotherapy has been considered controversial in patients with advanced NSCLC [9]. However, Williams et al. [17] reported a minimal survival advantage in unresectable limited-disease patients by comparing the best supportive treatment to cisplatin (CDDP) and vindesine (VDS) combination chemotherapy; in a large, prospective, randomized trial, Rapp et al. [15] demonstrated that combination chemotherapy (vs best supportive treatment) can improve the overall survival of treated patients with NSCLC.

Several investigators have recently reported objective response rates ranging from 20% to 60% using CDDP-containing combinations, mainly with VDS, vinblastine, or etoposide (VP-16) [1]. Higher doses of CDDP appear to be associated with improved results; in a randomized study comparing a combination of 60 mg/m^2 VDS and 120 mg/m^2 CDDP, Gralla et al. [8] found a significantly

* Published in part in Seminars in Oncology, suppl., Dec. 88 in the proceedings of the Perugia International Cancer Conference I

** Professore' A. Contratto, Université di Perugia

Offprint requests to: Lucio Crino, Division of Medical Oncology, Policlinico Hospital, I-06100 Perugia, Italy

Table 1. Treatment regimen

		Dose	Schedule
R	CDDP	120 mg/m^2 i.v.	Day 1, every 3 weeks
A			
N	CDDP	Same as above	
D	VP-16	100 mg/m^2, i.v.	Days 1–3, every 3 weeks
O			
M	CCDP	Same as above	
I	VP-16	Same as above	
Z	MITO-C	10 mg/m^2, i.v.	Day 1, every 3 weeks ×3; Then every 6 weeks until a maximal dose of 100 mg has been achieved
E			
D			

MITO-C, mitomycin C

Table 2. Characteristics of evaluable patients

	CDDP	CCDD+VP-16	CDDP+VP-16 +MITO-C
Patients (n)	24	69	57
Median age, years	60	60	62
(range)	(47	–70)	(37
Sex:			
Men	24	66	54
Women	–	3	3
Performance status:			
0	–1	13 (54%)	41 (60%)
2	–3	11 (46%)	28 (41%)
NSCLC-limited disease			
(III)	7 (29%)	29 (42%)	15 (26%)
Histology:			
Epidermoid carcinoma	14 (58%)	40 (58%)	36 (63%)
Adenocarcinoma	9 (37.5%)	18 (26%)	19 (33%)
Large-cell carcinoma	1 (4%)	6 (9%)	–
Unclassified	–	5 (7%)	2 (3.5%)

improved median survival for responders to the high-dose regimen. Similarly, Elliot [6] has shown improvement in both survival and response rate for patients receiving CDDP and VDS vs VDS alone. In our previous phase II experiences [3] we observed a 26% response rate with CDDP and VP-16 and a 38% response rate with CDDP, VP-16, and mitomycin C. With this data as background, in December 1984 we started a prospective, randomized study to evaluate the activity of high-dose CDDP as a single drug vs CDDP plus VP-16 and to determine whether any improvement in response rate, duration of remission or survival could be obtained with a more aggressive three-drug regimen consisting of CDDP, VP-16, and mitomycin C. When this trial was designed, no randomized studies comparing CDDP monochemotherapy vs CDDP combination chemotherapy had been reported.

Patients and methods

All patients had histologically proven NSCLC. Entry into the trial was based on the diagnosis made by the pathologist examining the original biopsy specimen; the histological diagnosis was confirmed at the University of Perugia. Patients with advanced limited disease (AJC, stage III

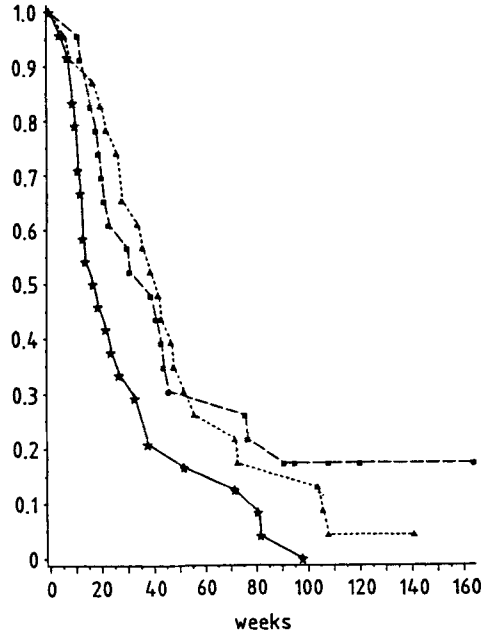

Fig. 1. Survival curves for CDDP plus VP 16 and Mito-C v. CDDP plus VP 16 vs CDDP alone, at the time of first interim analysis. P <0.01. CDDP VP 16 Mito-C ■–■–■; CDDP VP 16 ▲..▲..▲; CDDP ✳–✳–✳

Mo) that was unsuitable for surgery or extensive disease (AJC, stage III, M1) [13] were accrued into the study. Using the 1987 AJC staging system, these patients would have stage IIIB and stage IV disease, respectively [12]. All patients gave informed consent, and all had measurable or evaluable disease. All had an ECOG performance status (PS) of 0–3, were ≤70 years old, and had received no prior radiotherapy or chemotherapy. Patients with brain metastasis were not excluded. Eligible patients had normal baseline blood counts (WBC, >3× 10^9/l; platelet count, >100× 10^9/l), renal function (serum creatinine, <1.5 mg%), and hepatic function (bilirubin, <2.0 mg%). Bronchoscopy was carried out if clinically indicated. Patients with active cardiac disease, i.e., congestive heart failure, myocardial infarction (within 6 months of entry), and uncontrolled hypertension were excluded.

Study design and treatment. The study design is shown in Table 1. The endpoints studied included the response rate, duration of response, and survival. Chemotherapy was carried out until disease progression or for a maximum of 8 months, at which point all therapy was discontinued. Patients with metastasis to the brain received concurrent radiotherapy.

There were no dose reductions for transient renal toxicity, nausea and vomiting, or grade 1 neurotoxicity. Doses of chemotherapy were adjusted on the basis of nadir and treatment-day blood counts, even after complete recovery. If nadir values after the first treatment reached a WBC count of <1,000/mm^3 and/or a platelet count of <70,000/mm^3, we reduced the next scheduled dose by 30%. Prior to CDDP, patients received i.v. hydration with 1,500 ml normal saline +20 mEq KCl over 90 min, followed by 12.5 g mannitol (i.v. push) and 1,000 ml normal saline given over 2 h. All patients were kept in the hospital during the 2-day treatment.

At the beginning of each cycle of chemotherapy, patients were evaluated for response by physical examination and chest X-ray. In patients with measurable disease, a complete clinical response (CR) was defined as the complete disappearance of all tumor lesions, lasting at least 4 weeks (including bronchoscopy, if indicated); a partial response (PR) was defined as a reduction by ≥ 50% in the product of the longest perpendicular diameters of the indicator lesions, as determined by direct measurement or computerized tomographic (CT) scanning. No new lesions or increases in the size of existing lesions could occur for 4 weeks. In patients with evaluable disease, a decrease in tumor size of ≥ 50%, agreed upon by three investigators, and the absence of new lesions were

Table 3. Results according to the regimen given

	CDDP	CDDP+VP-16	CDDP+VP-16 +MITO-C
Patients (*n*)	24	69	57
Response:			
CR	1 (4%)	3 (4%)	4 (7%)
PR	–	18 (26%)	11 (19%)
Overall PR	1 (4%)	21 (30%)	15 (26%)
Median duration of remission (months)	7	10	6
Median survival (weeks)	18	35	37

Table 4. Tumor response according to prognostic factors by treatment

	Response (CR+PR):		
	CDDP	CDDP/VP-16	CDDP/VP-16/ MITO-C
Performance status:			
0	–1	1/13 (8%)	15/41 (37%)
2	–3	0/11	6/28 (21%)
Disease stage:			
III Mo	1/7 (14%)	11/29 (38%)	5/15 (33%)
IV	0/17 (7%)	10/40 (25%)	10/42 (24%)
Tumor histology:			
Squamous carcinoma	1/14 (7%)	15/40 (37.5%)	12/36 (33%)
Adenocarcinoma	0/9	5/18 (28%)	3/19 (16%)
Large-cell carcinoma	0/1	1/6 (17%)	–

required for a PR [4]. Patients with stable disease (a reduction of $\leq 50\%$ in measurable indicator lesions) were considered to be nonresponders. The toxicity to chemotherapy was evaluated after each treatment cycle and graded according to WHO toxicity criteria.

Response duration was calculated from the time of remission to the time of disease progression. Survival was calculated from the initiation of chemotherapy to death. Survival estimates within the three treatment arms were compared by the Kaplan-Meier method, the log-rank test, and the generalized Wilcoxon test. The Cox regression model was used to evaluate the influence on survival of age, performance status, stage, and drug treatment after verification of the proportional hazard assumption effected by two different methods: (1) superimposition of Kaplan-Meier survival curves on Cox survival curves, and (2) parallelism between the log-log curves.

Results

Between December 1984 and December 1987, a total of 156 consecutive, previously untreated patients were enrolled in the trial. The distribution of all eligible patients and selected prognostic variables is detailed in Table 2. Of the 156 patients enrolled, 6 were ineligible (3.8%) due to refusal of treatment (2), loss to follow-up after the first cycle of treatment (2), and change of the diagnosis to small-cell carcinoma on pathologic review (2). Relevant prognostic factors were equally distributed among the three arms; although 42% (29) of the patients in the CDDP/VP-16 arm had stage III Mo disease, this difference

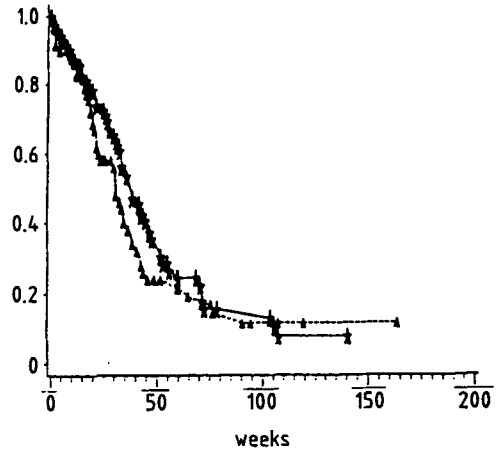

Fig. 2. Survival curves comparing combination chemotherapy arms: CDDP VP ▲–▲–▲ vs CDDP VP 16 Mito-C ▲..▲..▲ $P > 0.05$, not significant

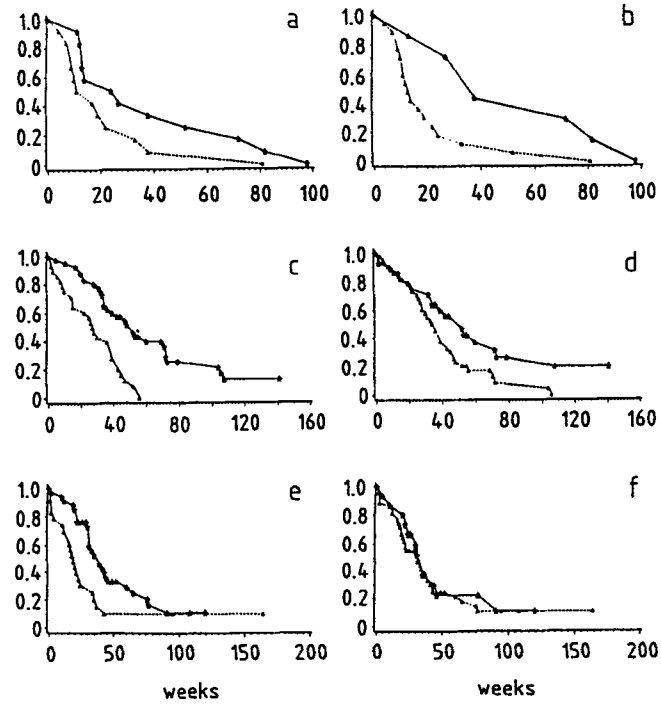

Fig. 3. Survival curves according to Performance status and stage of disease. P.S. 0–1 ✳–✳–✳ P.S. 2–3 ▲..▲..▲; stage III Mo ✳–✳–✳; stage IV ▲..▲..▲. Better survival was significantly correlated with good performance status in combination chemotherapy arms (a) CDDP: performance; (b) CDDP: stage; (c) CDDP+VP 16: performance; (d) CDDP+VP 16: stage; (e) CDDP+VP+Mito C: performance; (f) CDDP+VP 16+Mito C: stage. P <0.01 for performance; P >0.05 for stage

was not significant according to the chi-square test. Brain metastases were present at the time of diagnosis in 16% (4) of the patients in the CDDP arm, in 9% (6) in the two-drug arm, and in 10% (6) in the three-drug arm (not significant). Patients who died early (within 4 weeks of initiating treatment) were considered to be nonresponders.

After 71 patients had been randomized, we carried out a planned interim analysis (Fig. 1). According to treatment, the therapeutic results at this time showed response rates of 4% (1 CR) for the CDDP arm (95% confidence limit, 0.1%–21%), 39% (1 CR, 8 PRs) for the CDDP/VP-16 arm,

Table 5. Therapeutic response by disease sites

Disease sites	CR+PR:		
	CDDP	CDDP+VP-16	CDDP+VP-16 +MITO-C
Locoregional	1	20	14
Metastatic:			
Extrathoracic nodes		–	6
Contralateral lung		–	1
Skeleton		–	–
Liver		–	2
Brain		–	2
Soft tissues		–	2

Table 6. Relapse sites in 37 responders

Sites	CDDP	CDDP+VP-16	CDDP+VP-16 +MITO-C
Brain		–	4
Liver		–	4
Adrenal		–	
Bone		–	3
Nodes		–	3
Soft tissues		–	1
Lung		–	7

Table 7. Dose intensity

	Delivered dose/ expected dose (%)	Weekly dose (mg/m^2)
CDDP (monochemotherapy)	98	39.2
CDDP	82	32.8
VP-16	80	80.0
CDDP	65	28.0
VP-16	65	65.0
MITO-C	50	1.6

Table 8. Hematological toxicity

		CDDP	CDDP+VP-16	CDDP+VP-16 +MITO-C
Evaluable patients (n)		24	69	59
Grade	I	4 (16%)	12 (17%)	8 (13%)
	II	3 (12%)	9 (13%)	12 (20%)
	III	–	3 (4%)	6 (10%)
	IV	–	2 (3%)	10 (17%)

Table 9. Nonhematological toxicity

		CDDP	CDDP+VP-16	CDDP+VP-16 +MITO-C
Evaluable patients		24	69	59
Nausea, vomiting:				
Grade	I	3 (12%)	5 (7%)	6 (10%)
	II	4 (16%)	13 (19%)	7 (12%)
	III	–	1 (1%)	3 (5%)
	IV	4 (16%)	10 (14%)	7 (12%)
Nephrotoxicity		2 (8%)	2 (2%)	6 (10%)
Ototoxicity		4 (16%)	7 (10%)	4 (7%)
Neuropathy		–	3 (4%)	2 (3%)

and 39% (4 CRs, 5 PRs) for the CDDP/VP-16 mitomycin C arm. The difference in response rate evaluated by the chi-square test was highly significantly in favor of the combination-chemotherapy arms. Median survival was 18 weeks for the CDDP arm, 42 weeks for the CDDP/VP-16 arm, and 35 weeks for the CDDP/VP-16 mitomycin C arm. There was a significant difference ($P \leq 0.02$ in the log-rank test; $P \leq 0.01$ in the Wilcoxin test) in survival between the CDDP arm and the combination-chemotherapy arms, whereas the survival curves of the two combination-chemotherapy arms were not statistically significant.

After the interim analysis the study was continued with randomization, comparing CDDP/VP-16 vs CDDP/VP-16/mitomycin C; we also continued to analyze the CDDP arm for survival and toxicity. Table 3 shows the response rate, median duration of remission, and median survival of all 150 evaluable patients according to chemotherapy regimen. Overall, 21 of 69 patients (30%) treated with CDDP/VP-16 achieved an objective response (3 Crs, 18 PRs), with a median survival of 35 weeks (95% confidence limits, 19.9%–42.7%); 15 of 57 patients treated with CDDP/VP-16/mitomycin C (26%) achieved an objective response (4 CRs, 11 PRs), with a median survival of 37 weeks (95% confidence limits, 15.5%–39%). All responses occurred within 3 months of treatment.

Of the prognostic variables analyzed, good performance status (PS) and limited disease (stage III Mo) were associated with improved response rates and survival in all arms of the trial. Survival data were fitted to a Cox proportional-hazard linear model. Table 4 shows the prognostic variables used: (1) ECOG PS 0–1 vs 2–3, (2) stage III Mo vs stage III M1, (3) age, (4) tumor histology, and (5) drug treatment. PS 0–1 was highly significant for improved survival in all treatment arms ($P \leq 0.0006$). Responses were observed in 31% of patients with PS 0–1 vs 14% of those with PS 2–3. Similarly, the stage of disease was statistically significant ($P \leq 0.01$) for response rate and survival in all treatments. Of 51 patients with stage III Mo, 17 (33%) obtained an objective response, compared with a response rate of 20% in patients with stage III M1. Survival curves for all groups are shown in Figs. 2 and 3. Actuarial 1-year survival was 15% on the CDDP arm, 31% on the CDDP/VP-16 arm, and 32% on the CDDP/VP-16/mitomycin C arm. At 2 years, 23 patients (14%) are still alive.

Table 5 shows responses according to primary disease sites. Locoregional primary disease responded best to the chemotherapy, although responses were seen in distant sites to an equivalent degree. Of the 37 patients who responded to chemotherapy (CRs, PRs), the first site of relapse was distributed as shown in Table 6. Organ-site relapses were similar in both multimodal chemotherapy arms.

Dose intensity was calculated in two ways for the time during which patients were on therapy [10]. In the first approach, the amount of each drug was related to the

amount that would have been given if the patient had been treated with full protocol doses throughout the time on treatment. In the second, the weekly dose (mg/m^2) for each drug was calculated. The values obtained are shown in Table 7. Patients were treated with 80% doses of CDDP/VP-16, whereas dose reduction was substantially higher for the mitomycin C-containing regimen.

The chemotherapy-related toxicities (WHO criteria) are listed in Tables 8 and 9 for each regimen. The analysis is based on 152 patients who were evaluable for toxicity. Grade III and IV leukopenia or thrombocytopenia occurred in 7% of patients in the CDDP/VP-16 arm and in 27% in the CDDP/VP-16/mitomycin C arm (P <0.05). Grade III and IV vomiting, renal toxicity, and neurotoxicity occurred with equal frequency in each therapy arm. There were no treatment-related deaths. An analysis of toxicity related to the initial performance status showed no significant differences in toxicity between the performance status and disease stage.

Discussion

This Umbrian Lung Cancer Group trial showed that chemotherapy can improve the survival of patients with advanced NSCLC; a CR rate of 4.6% was obtained, with 14% of all patients surviving for 2 years. Clearly, the data show that the patients most likely to benefit from chemotherapy are those with stage III Mo disease and stage III M1 patients with a good performance status (ECOG 0–1).

Our data confirm the experience of Elliot [6], who showed improved survival and response rates in patients receiving CDDP/VDS vs VDS alone. Williams et al. [17] have reported that patients with locally advanced NSCLC who are treated with CDDP/VDS have a modest survival benefit over patients treated with supportive care. Similar results were obtained by the National Cancer Institute of Canada [15] and the group of Cartei [2]. Gralla et al. [8] reported that CDDP (120 mg/m^2) plus VDS resulted in a 43% response rate in NSCLC patients, with a median survival of 21.7 months in responders. Ruckdeschel et al. [16] reported the ECOG experience; however, they obtained a 26-week median survival in patients treated with CDDP/VDS [7]. Einhorn et al. [5] stated that CDDP/VDS yielded a 27% response rate and a median survival of 26 weeks. Rapp et al. [15], also using CDDP/VDS, reported a 25% response rate and a median survival of 34.4 weeks. Using CDDP/VP-16, the present study resulted in a response rate of 30%, with a median survival of 35 weeks. The discrepancies in the reported results are best explained by patient selection, the drugs used, and, perhaps, CDDP dose intensity.

In this trial, chemotherapeutic toxicity was considerable only in the mitomycin C-containing arm, with 27% of patients developing severe hematological toxicity. It would appear that the addition of mitomycin C to CDDP/VP-16 is not advisable.

The present trial indicates that chemotherapy can improve the overall survival in selected patients with unresectable NSCLC of stage III Mo and stage III M1 (with a good performance status). Given our results, we would support recommendations similar to these proposed by Mulshine et al. [14] and Rapp et al. [15]. NSCLC patients with a good performance status should be treated with CDDP/VP-16 and carefully evaluated for response and toxicity.

References

1. Bonomi P (1986) Brief overview of combination chemotherapy in non-small cell lung cancer. Semin Oncol 8: 89–91
2. Cartei G (1988) Evaluation of synergy with cisplatin in non-small lung cancer: interim report from a multicenter study. Proc Am Soc Clin Oncol 7: 198
3. Davis S, Tonato M, Crinò L, Colozza M, Lubansky K, Grignani F (1986) Cisplatin, etoposide and mitomycin in the treatment of non-small cell lung cancer. Cancer 58: 1018–1021
4. Eagan RT, Fleming TR, Shoonover V (1979) Evaluation of response criteria in advanced lung cancer. Cancer 44: 1125–1128
5. Einhorn LH, Loeher PJ, Williams DS, Meyers S, Gabrys T, Nattan SR, Woodburn R, Drasga R, Songer J, Fisher W, Stephens D, Hui S (1986) Random prospective study of vindesine vs vindesine plus high-dose cisplatin vs vindesine plus cisplatin plus mitomycin C in advanced non-small cell lung cancer. J Clin Oncol 4: 1037–1043
6. Elliot JA, Ahmedzai S, Hole D, Dorward AJ, Stevenson RD, Kage SB, Banham SW, Stack BHR, Calman KC (1984) Vindesine and cisplatin combination chemotherapy compared with vindesine as a single agent in the management of non-small cell lung cancer. A randomized study. Eur J Cancer Clin Oncol 20: 1025–1032
7. Finkelstein DM, Ettinger DS, Ruckdeschel JC (1986) Long term survivors in metastatic non-small cell lung cancer: an ECOG study. J Clin Oncol 4: 702–709
8. Gralla RJ, Casper ES, Kelsen DP, Braun DW, Dukeman ME, Martini N, Young CW, Golbey RB (1981) Cisplatin and vindesine combination chemotherapy for advanced carcinoma of the lung: a randomized trial investigating two dosage schedules. Ann Intern Med 95: 414–420
9. Hansen HH (1987) Advanced non-small cell lung cancer: to treat or not to treat? J Clin Oncol 5: 1711–1712
10. Hayniuk W, Bush H (1984) The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 2: 1281–1288
11. Lanzotti VJ, Thomas DR, Boyle LE, Smith LT, Gehan EA, Samuels ML (1977) Survival with inoperable lung cancer. An integration of prognostic variables based on simple clinical criteria. Cancer 39: 303–313
12. Mountain CF (1986) A new international staging system for lung cancer. Chest 89 (suppl 4): 225–233
13. Mountain CF, Carr DT, Anderson WAS (1979) Staging of lung cancer 1979. American Joint Committee for Cancer, Staging and End Results Reporting. Task Force on Lung Cancer, Chicago
14. Mulshine JL, Gatstein E, Ruckdeschel JC (1986) Treatment of non-small cell lung cancer. J Clin Oncol 4: 1704–1715
15. Rapp E, Pater JL, Wilan A, Cormier Y, Murray N, Evans KW, Hodson ID, Clark DA, Feld R, Arnold AM, Ajoub JI, Wilson KS, Latreille J, Wierzbicki RF, Hill DP (1988) Chemotherapy can prolong survival in patients with advanced non-small cell lung cancer. Report of a Canadian multicenter trial. J Clin Oncol 6: 633–641
16. Ruckdeschel JC, Finkelstein DM, Ettinger DS, Creech RH, Mason BA, Joss RA, Vogl S (1986) A randomized trial of the four most active regimens for metastatic non-small cell lung cancer. J Clin Oncol 4: 14–22
17. Williams CJ, Woods R, Levi J, Page J (1988) Chemotherapy for non-small cell lung cancer: a randomized trial of cisplatin/vindesine vs no chemotherapy. Seminars in Oncology 15 (suppl 7): 58–61