Eur J Cancer Clin Oncol, Vol. 22, No. 8, pp. 963–970, 1986.
Printed in Great Britain.

0277-5379/86$3.00+0.00
Pergamon Journals Ltd.

Vindesine, Cisplatin, and Bleomycin Combination Chemotherapy in Non-Small Cell Lung Cancer: Survival and Quality of Life

W. BAKKER,* A. T. VAN OOSTEROM,† N. K. AARONSON,‡ F. J. M. VAN BREUKELEN,* M. C. BINS* and J. HERMANS§

*Departments of *Pneumology, †Clinical Oncology, and §Medical Statistics, State University Hospital, Leiden, The Netherlands, ‡E.O.R.T.C. Study Group on Quality of Life, Amsterdam, The Netherlands*

Abstract—*Although combination chemotherapy is applied on a large scale in advanced non-small cell lung cancer (NSCLC), we still lack evidence indicating in which subsets of patients survival or quality of life might be improved. We studied these issues among a sample of 28 NSCLC patients with a high performance status, who received a tri-weekly vindesine, cisplatin, and bleomycin combination. Treatment was extended for an additional two courses only if a response was observed after the initial three courses.*

An overall response rate of 13/27 evaluable patients (48%) was found (complete response 1/27 and partial response 12/27) with a median response duration of 24 weeks. Median survival was 33 weeks (47 for responders and 26 for non-responders).

Toxicity was primarily related to cisplatin, including severe nausea and vomiting and nephrotoxicity in 68% and 21% of the patients, respectively. Performance status and body weight dropped significantly during chemotherapy both among responders and non-responders. Performance status after discontinuation of chemotherapy approached pre-treatment scores in responders only.

While the antitumour effect of this drug combination was confirmed, we conclude that treatment-associated toxicity and deterioration of the patients' well-being offset any potential survival advantage for the majority of patients.

INTRODUCTION

NEARLY 50% of patients with non-small cell lung cancer (NSCLC) have distant metastases at the time of diagnosis. Another 40% develop locally recurrent or distant spread of their disease following initial treatment with surgery or radiation therapy [1]. The need for an effective systemic treatment for this disease is therefore clear. Unfortunately, unlike small cell lung cancer, clinical trials using chemotherapy for the treatment of NSCLC have only recently indicated some progress in the development of drug combinations which may benefit selected groups of patients. With the wide variation in response rates and the modest prolongation in survival in reported studies, none of the available combination chemotherapy regimens can be recommended as standard therapy for inoperable NSCLC [2]. Because of the poor results with standard chemotherapeutic regimens [3] investigations have focused on new agents.

Vindesine (VDS) has been reported in different institutions to produce response rates of 20–25% [4–8]. Therefore it is often considered to be the most active single agent against NSCLC [9], although lower response rates have also been reported [10–14]. Response rates with cisplatin (CDDP) have varied between 0 and 33%, with an overall response rate of 14% in 338 treated patients [15–21]. Combination of the two drugs resulted in a 33–43% response rate in previously untreated patients (14,22]. Responding patients receiving a high dose of CDDP had a 22-month median survival time [22]. The VDS–CDDP combination appeared superior to VDS alone in a randomized study [14]. The addition of cyclophosphamide with or without doxorubicin to the VDS–CDDP combination yielded similar response rates and remission durations as VDS–CDDP alone [23]. Bleomycin (BLM) has shown only marginal effectiveness as a single agent in lung cancer [24] but its inclusion in older regimens led to an increase in

Accepted 2 January 1986.
Address reprint requests to: Dr. W. Bakker, Department of Pulmonology, University Hospital, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands.

response rate [25]. From the experience in various other tumours BLM is known to be safe and effective when given as a low-dose continuous infusion. In combination with CDDP promising results have been found in patients with head and neck, oesophageal, testicular, and lung cancer [26–29]. Based on an early report on the effectiveness of the VDS–CDDP combination in NSCLC [30] we added BLM to this combination in order to assess the effect on response and survival.

Despite the existing WHO guidelines for the management of cancer clinical trials [31], the studies mentioned above did not, as a rule, report on the effect of treatment on the functional status of the patients [4–30]. Thus, the question remains as to whether the use of combination chemotherapy improves the quality of life in responding patients with NSCLC. In this report the effects are presented of the combination chemotherapy with VDS–CDDP–BLM on response, survival, and quality of life in patients with advanced NSCLC.

PATIENTS AND METHODS

Between October 1980 and September 1982, all consenting patients with histologically or cytologically confirmed advanced squamous cell, adeno-, or large cell undifferentiated carcinoma of the lung referred to the Department of Pulmonology of the Leiden University Hospital were entered into the study. Histological typing was in accordance with the World Health Organization classification [32]. All patients had stage III or stage IV disease according to the UICC criteria [33], and were not candidates for surgery or curative radiotherapy. All patients had objectively measurable lesions, a Karnofsky performance status greater than 50%, and had not received prior chemotherapy or radiation to the areas of measurable or evaluable disease. Other entry criteria included age less than 70 yr, absence of CNS involvement, no complaints necessitating radiotherapy, creatinine clearance $\geq$ 80 ml/min, leucocyte count $\geq 4 \times 10^9$/l, and platelet count $\geq 120 \times 10^9$/l.

Pre-treatment evaluation included a history, physical examination, blood-cell counts, serum calcium and electrolytes, creatinine clearance, liver function tests, urine analysis, and bronchoscopy. Baseline chest X-ray films, audiograms, and pulmonary function studies including measurements of diffusing capacity of carbon monoxide (CO) were obtained and were repeated before each course of treatment. Radionuclide scans were performed only when indicated. The administration of chemotherapy required a 3-day hospitalization. Vindesine (VDS) 2 mg/m^2 was given on day 1, and 1 mg/m^2 on day 3 as a bolus injection into the tube of a running infusion. The dose schedule of vindesine in two divided doses with a time interval of two times the terminal half-life [34] was derived from the same principles as applied with vinblastine in testicular cancer, and $VP_{16\text{-}213}$ in small cell lung cancer. A split dose of these mitotic spindle inhibitors resulted in higher response rates [35,36]. Bleomycin (BLM) 15 mg was given on day 1 as a continuous i.v. infusion over 18 hr. After ample prehydration with 4 l, beginning 24 hr before cisplatin, all patients received cisplatin (CDDP) 100 mg/m^2 i.v. in 1 l of normal saline over 4 hr followed by an additional 3 l of normal saline over the next 20 hr with mannitol-induced diuresis. This regimen was repeated every 3 weeks. Antiemetic treatment consisted of domperidone 10 mg i.v. every 4 hr. Aminoglycosides and other nephrotoxic drugs were avoided. Response and toxicity criteria were used as recommended by the WHO [31]. A partial response (PR) was determined mainly on chest films. For documentation of a complete response (CR) a bronchoscopy was mandatory at reassessment after three courses of chemotherapy. Only patients with a response after three courses received two more courses. Chemotherapy was discontinued in case of progressive disease or unacceptable toxicity. A leucocyte nadir $< 1.0 \times 10^9$/l or a platelet nadir $< 20 \times 10^9$/l during the first treatment cycle required a 25% dose reduction of VDS in subsequent courses. The VDS and CDDP dosages were reduced by 50% and 25%, respectively, if the leucocyte count was 2.0–2.9 $\times 10^9$/l or the platelet count was 100–150 $\times 10^9$/l at the start of a new cycle. If at restart the leucocytes were $<2.0 \times 10^9$/l and/or the platelets were $< 100 \times 10^9$/l chemotherapy was postponed until recovery above these values. CDDP was discontinued if the creatinine clearance fell below 50 ml/min. BLM was stopped if the vital capacity dropped below 80% of the baseline value.

Performance status was graded according to the Karnofsky index (KI) [37]. Patients were asked to rate their anticipated difficulties with chemotherapy 24 hr before each treatment course. Scale values included: 'no problems', 'easy to cope with', 'tolerable', 'dreadful', and 'intolerable'. The latter score required a permanent cessation of treatment.

Survival and time to progression were calculated according to the Kaplan–Meier method [38]. Subgroups were compared with the log rank test [39] and two-tailed P values were given. Changes in KI and body wt over time were compared and P values were derived with Student's t-test on paired observations.

RESULTS

Patients' characteristics and evaluability

Clinical characteristics of the 28 patients who consented to be entered into the study are pre-

Table 1. *Patients' characteristics at entry into the study*

Age	
Mean (range)	56.5 (40–69)
Sex	
Male	26 (93%)
Female	2 (7%)
Histologic type	
Squamous cell	16 (57%)
Adeno	10 (36%)
Large cell undiff	2 (7%)
Stage UICC	
III: M_0 with T_3 or N_2	12 (43%)
IV: M_1 disease	16 (57%)
Karnofsky index	
mean (range)	88 (60–100)

sented in Table 1. Twelve patients had intrathoracic disease only. The sites of distant metastases in the remaining 16 patients included lymph nodes (two patients), bone (six patients), liver (one patient), and other sites (nine patients). Seven patients had lost more than 5% of body wt in the previous 6 months.

Twenty-eight patients were evaluable for toxicity and 27 patients for response. One patient was not evaluable for response due to his early toxic death. One patient's death was considered unrelated to the tumour or to the treatment but possibly related to his diabetes (no autopsy was performed). All other patients died due to malignant disease.

Response and survival

One patient obtained a CR which lasted only 14 weeks. Twelve of the 27 evaluable patients achieved a PR. Responses were observed within 6 weeks from the initiation of treatment. The median period of response was 24 weeks (range 9–43 weeks). Although responses did not vary significantly among histologic types, the numbers are too small to draw any conclusions (see Table 2). No statistically significant correlation was found between response and performance status or weight loss before the start of treatment. The median duration of survival was 33 weeks (47 weeks for responders and 26 weeks for non-responders, $P = .08$, see Fig. 1). Survival did not differ significantly between histologic types, but again, the numbers are too small to draw any conclusions.

Toxicity

Patients received a mean number of 3.2 courses of chemotherapy (range 1–5). A leucocyte nadir of 2.0–2.9 $\times$ 10^9/l was observed only once, and four patients required a dose reduction due to leucopenia at the start of a new cycle (see Table 3). Dose reductions due to thrombocytopenia were not needed. Nephrotoxicity with a fall in creatinine clearance to 50–80 ml/min occurred in 11 patients. In six patients the clearance fell below 50 ml/min without recovery, requiring permanent cessation of treatment. One of the patients started vomiting severely at home after the first course of che-

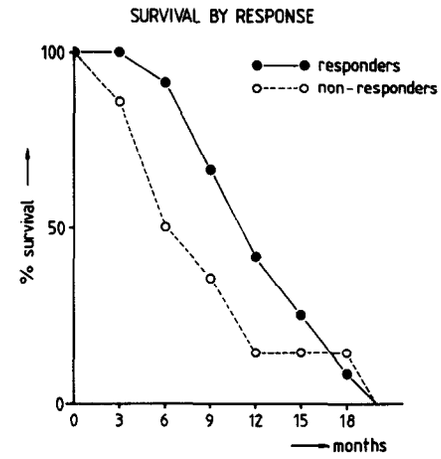

Fig. 1. *Actuarial survival of the* 13 *responding and* 14 *non-responding patients with non-small cell lung cancer treated with vindesine, cisplatin, and bleomycin. The difference is not significant* ($P = .08$).

Table 2. *Response by histologic type in* 27 *evaluable patients*

Histologic type	No. patients	CR	PR	NC	PD
Squamous cell ca.	15		7	2	6
Adenoca.	10	1	3	1	5
Large cell undiff. ca.	2		2		
Total	27	1 (3.7%)	12 (44.4%)	3 (11.1%)	11 (40.7%)

CR = Complete response
PR = Partial response
NC = No change
PD = Progressive disease

*Table 3. Treatment-related toxicity**

	No. of patients	(%)
Leucopenia		
nadir after 1st course 2.0–2.9 × 10^9/l	1	(4)
at start of a new cycle 2.0–2.9 × 10^9/l	4	(15)
Nephrotoxicity		
creatinine clearance 50–80 ml/min	11	(39)
creat. clear. < 50 ml/min (incl. one death)	6	(21)
Nausea and vomiting		
mild (nausea only)	3	(11)
moderate (transient vomiting)	6	(21)
severe (despite therapy)	19	(68)
Alopecia		
partial	14	(54)
total	6	(23)
Peripheral neuropathy		
mild paraesthesiae	8	(30)
Ototoxicity		
audiography (clinically imperceptible)	9	(33)
Pulmonary toxicity		
CO diffusing capacity < 80% of baseline	10	(37)
X-ray changes	3	(11)

*More than one toxicity may occur in the same patient

motherapy, although he did not report this problem until end-stage renal failure had developed. He died soon thereafter. In four patients chemotherapy was permanently discontinued because of nephrotoxicity (in two after two, in one after three, and in one after four courses). In one patient creatinine clearance fell below 50 ml after the fifth course.

Severe nausea and vomiting occurred in 68% of the patients. All patients were treated with domperidone every 4 hr intravenously from the initiation of chemotherapy. This was often combined with levopromazine 25 mg orally before the start of chemotherapy to make the treatment more tolerable. Total or partial alopecia occurred in 77% of patients. Mild peripheral neuropathy was seen in 26% of the patients and consisted of minor paraesthesiae not requiring dose reductions. Mild high pitch hearing loss was audiographically recorded in 33% of the patients. No clinical hearing loss was noticed.

Pulmonary toxicity defined as a decrease in CO-diffusing capacity of more than 20% was found in 37% of the patients. In three cases, pulmonary toxicity preceded chest X-ray abnormalities attributable to BLM toxicity. A fall in vital capacity, crackles or dyspnoea related to BLM were not observed in our patients. Skin rash, stomatitis, or allergic reactions also did not occur.

Patients' tolerance of treatment, performance status and body wt

One patient refused further chemotherapy after two courses because he could not cope with the nausea and vomiting. Six patients described their treatment as dreadful but nevertheless decided to continue. Six patients found their treatment tolerable and thirteen reported coping rather easily with the problems of chemotherapy. The patients' self-reported tolerance of treatment, scored in the outpatient department, was not correlated significantly with the degree of vomiting scored during hospitalization, response, or performance status.

The performance status fell during chemotherapy from a mean KI of 88 to 75% ($P < .01$). Among non-responders KI fell from 89 to 73% ($P = .001$) and among responders from 88 to 77% ($P < .05$). Only one symptomatic patient's KI rose during chemotherapy (from 60 to 80%) due to relief of his metastatic bone pain. KI among non-

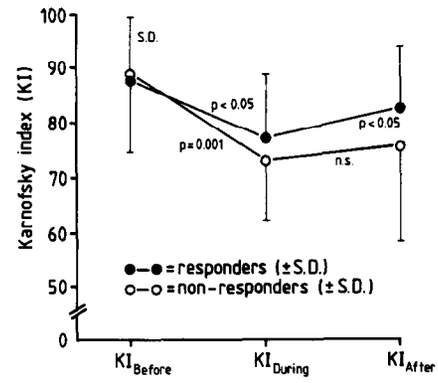

Fig. 2. The mean performance status measured by the Karnofsky index (KI) in responders and non-responders before *chemotherapy*, during *chemotherapy, and* 1 month after *completion of the chemotherapy* ± S.D. *The statistical significance of the changes within each group is shown in the graph.*

responders remained at the same mid-treatment level (75%) 1 month after completion of the last course of chemotherapy. Among responders, post-chemotherapy KI approached baseline values (see Fig. 2). A comparison of the changes in KI in responders and non-responders did not show significant differences at any time before, during or after chemotherapy.

The body wt among responders fell from a mean baseline value of 77.1 to 73.6 kg at the end of treatment ($P < .10$, see Fig. 3). Among non-responders the mean body wt fell from 74.2 to 71.1 kg ($P < .05$). The range in the change in body wt was −17–+5 kg in responders and −10–+3 kg in non-responders. The difference between the changes in body wt among responders and non-responders was not statistically significant.

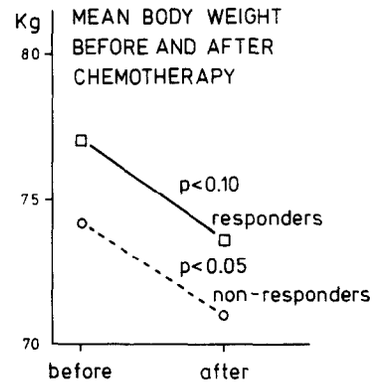

Fig. 3. The mean body wts in responders and non-responders before *and* 1 month after *completion of the chemotherapy. The statistical significance of the changes within each group is shown in the graph.*

DISCUSSION

The antitumour effect of the combination of VDS, CDDP and BLM was confirmed in our series of 28 patients with advanced NSCLC cancer. After the initiation of our study the results of a study using the same combination chemotherapy were reported with a response rate of 38% [40]. This result appears to be similar to the response rate of 48% in our patients.

An issue not addressed in the current study is whether response to chemotherapy leads to a survival advantage in patients with NSCLC [9,41]. The median survival among inoperable lung cancer patients with a KI of 90% from the Veterans Administration Lung Group data base was 27 weeks [42]. This does not appear to be substantially different from the 33 weeks observed in our study. The type of chemotherapy used in our study apparently has no major impact on survival in NSCLC. This is underscored by a recent randomized study showing that cisplatin in combination with vindesine does have an antitumour effect but that it does not prolong survival [43]. The updated results of this trial continue to show no survival benefit for patients receiving chemotherapy, notwithstanding a response rate of 32% [44]. In addition, our patients spent an average of 10 weeks, i.e. 30% of the survival time, on protocol treatment.

Clinically important toxicity was related primarily to CDDP. Nephrotoxicity occurred despite prehydration and mannitol-induced diuresis, causing an irreversible fall in creatinine clearance below 50 ml/min in six patients (21%), including one toxic death. Itri *et al.* observed three drug-related deaths due to renal failure in the treatment of 54 patients with the same drug combination [40]. They speculated that the addition of BLM increases the CDDP–related nephrotoxicity in this group of older patients. Chemotherapy-induced nausea and vomiting were ameliorated by the use of antiemetics but nevertheless remained clinically important. Nausea and vomiting scores during admission did not correlate with the patients' self-reported tolerance of the regimen. This unexpected lack of association might be accounted for by the fact that tolerance of chemotherapy was based on patient self-report data, while nausea and vomiting scores were derived from nursing staff ratings [45]. Other toxicities were not of major clinical importance, although ototoxicity was recorded audiographically in 33% of the patients. While pulmonary toxicity was not noted clinically, a detectable fall in pulmonary CO-diffusing capacity was observed in 37% of the patients. Taking into account the low total dosage of BLM given to our patients, this figure probably represents many false positive results as reported by others [46]. A fall in diffusing capacity preceded possible BLM-related X-ray changes in three patients. No lung biopsies were obtained for histological confirmation of BLM toxicity.

Performance status as measured by the Karnofsky Index (KI) fell significantly during treatment. A change of KI of the magnitude observed may seem modest, but is still clinically important [42]. Among responders KI rose again to baseline values after discontinuation of treatment. Among non-responders it remained at the same lower level but did not continue to decline after discontinuation of treatment. This suggests that the toxicity of the treatment had greater impact on peformance status than did tumour-associated symptoms, even among non-responders. Only one symptomatic patient's performance status rose during chemotherapy due to relief of his metastatic bone pain. The deterioration of the patients' well-being during treatment was further illustrated by a fall in body weight. The similarity in weight loss among responders and non-responders suggests that it was related to the treatment rather than tumour-associated. Only very few studies in the lung

cancer literature report how seriously the toxicity of treatment can affect the patient's quality of life [47,48]. Yet, special attention to quality of life issues would seem to be particularly important in the care of patients who are treated palliatively without expectation of cure [49].

In a selected group of high performance status patients such as those in the present study we feel that, in the absence of symptoms, little can be gained by administering a toxic regimen such as the VDS–CDDP–BLM combination. Until more effective chemotherapy can be developed that substantially prolongs survival, toxic regimens as used in this study will probably only benefit those responding patients whose symptoms are relieved by the treatment [50]. The dilemma is that withholding treatment until symptoms appear may result in a deterioration of performance status, and thereby result in a lower response rate [22]. It may be appropriate to treat asymptomatic patients as long as this occurs in the framework of a well-planned clinical study.

In conclusion, while we could confirm the anti-tumour effect of the drug combination VDS–CDDP–BLM, any potential survival advantage was, for the majority of the patients, offset by the toxicity and duration of treatment as well as the deterioration of the patients' well-being associated with the treatment. Asymptomatic patients with advanced NSCLC are not likely to benefit from such a toxic regimen and should probably not be treated with this drug combination.

REFERENCES

1. Hande KR, Malcolm AW. Chemotherapy and radiation therapy of non-small cell lung carcinoma. In: Greco FA, ed. *Biology and Management of Lung Cancer*. Boston, Martinus Nijhoff, 1983, 191–217.
2. Hoffman PC, Bitran JD, Golomb HM. Chemotherapy of metastatic non-small cell bronchogenic carcinoma. *Semin Oncol* 1983, **10**, 111–122.
3. Bleehen NM. Management of inoperable squamous cell, adeno- and large cell carcinoma. In: Hansen HH, Rørth M, eds. *Lung Cancer* 1980, II *World Congress on Lung Cancer Copenhagen*. Amsterdam, Excerpta Medica, 1980, 93–112.
4. Gralla RJ, Raphael BG, Golbey RB, Young CW. Phase II evaluation of vindesine in patients with non-small cell carcinoma of the lung. *Cancer Treat Rep* 1979, **63**, 1343–1346.
5. Østerlind K, Hørbov S, Dombernowsky P, Rørth M, Hansen HH. Vindesine in the treatment of squamous cell carcinoma, adenocarcinoma, and large cell carcinoma of the lung. *Cancer Treat Rep* 1982, **66**, 305–309.
6. Luedke SL, Luedke DW, Petruska P, *et al.* Vindesine monochemotherapy for non-small cell lung cancer: a report of 45 cases. *Cancer Treat Rep* 1982, **66**, 1409–1411.
7. Furnas BE, Williams SD, Einhorn LH, Cobleigh MA. Vindesine: an effective agent in the treatment of non-small cell lung cancer. *Cancer Treat Rep* 1982, **66**, 1709–1711.
8. Luedke DW, Luedke SL, Petruska P, *et al.* A randomized prospective study of vindesine versus doxorubicin and cyclophosphamide in the treatment of epidermoid lung cancer. *Cancer* 1983, **51**, 778–782.
9. Hansen HH, Rørth M. Lung cancer. In: Pinedo HM, Chabner BA, eds. *Cancer Chemotherapy Annual* 6. Amsterdam, Elsevier, 1984, 299–321.
10. Mattson K, Holsti LR, Gröhn R, *et al.* Experience with vindesine in the treatment of lung cancer. In: *Abstracts II World Conference on Lung Cancer Copenhagen*. Amsterdam, Excerpta Medica, 1980, 234.
11. Vogelzang NJ, Peterson BA, Kennedy BJ, *et al.* Vindesine in bronchogenic carcinoma: a phase II trial. *Am J Clin Oncol* 1982, **5**, 41–44.
12. Hutcheson AW, Palmer JBD, Pratt MA, Clark RA. Phase II evaluation of vindesine in non-small cell bronchogenic carcinoma. *Cancer Treat Rep* 1983, **67**, 1041–1042.
13. Jewkes J, Harper PG, Tobias JS, *et al.* Comparison of vincristine and vindesine in the treatment of inoperable non-small cell bronchial carcinoma. *Cancer Treat Rep* 1983, **67**, 1119–1121.
14. Elliot JA, Ahmedzai S, Hole D, *et al.* 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* 1984, **20**, 1025–1032.
15. Rossof AH, Bearden JD, Coltman CA. Phase II evaluation of cis-diammine-dichloroplatinum (II) in lung cancer. *Cancer Treat Rep* 1976, **60**, 1679–1680.
16. Britell JC, Eagan RT, Ingle JN, *et al.* *Cis*-dichlorodiammineplatinum (II) alone followed by adriamycin plus cyclophosphamide at progression versus *cis*-dichlorodiammine-platinum (II), adriamycin, and cyclophosphamide in combination for adenocarcinoma of the lung. *Cancer Treat Rep* 1978, **62**, 1207–1210.
17. Casper ES, Gralla RJ, Kelsen DP, *et al.* Phase II study of high-dose *cis*-dichlorodiammineplatinum (II) in the treatment of non-small cell lung cancer. *Cancer Treat Rep* 1979, **63**, 2107–2109.
18. De Jager R, Longeval E, Klastersky J. High-dose cisplatin with fluid and mannitol-induced diuresis in advanced lung cancer: a Phase II clinical trial of the EORTC Lung Cancer Working Party (Belgium). *Cancer Treat Rep* 1980, **64**, 1341–1346.

19. Vogl SE, Berenzweig M, Camacho F, *et al.* Efficacy study of intensive cisplatin therapy in advanced non-small cell bronchogenic carcinoma. *Cancer* 1982, **50**, 24–26.
20. Bhuchar VK, Lanzotti VJ. High-dose cisplatin for lung cancer. *Cancer Treat Rep* 1982, **66**, 375–376.
21. Panettiere FJ, Vance RB, Stuchey WJ, *et al.* Evaluation of single-agent cisplatin in the management of non-small cell carcinoma of the lung: a Southwest Oncology Group Study. *Cancer Treat Rep* 1983, **67**, 399–400.
22. Gralla RJ, Casper ES, Kelsen DP, *et al.* Cisplatin and vindesine combination chemotherapy for advanced carcinoma of the lung: a randomized trial investigating two dosage schedules. *Ann Intern Med* 1981, **95**, 414–420.
23. Kelsen D, Gralla R, Stoopler M, *et al.* Cisplatin, doxorubicin, cyclophosphamide, and vindesine combination chemotherapy for non-small cell lung cancer. *Cancer Treat Rep* 1982, **66**, 247–251.
24. Blum RH, Carter SK, Agre K. A clinical review of bleomycin – a new neoplastic agent. *Cancer* 1973, **31**, 903–914.
25. Livingston RB, Heilbrun L, Lehane D, *et al.* Comparative trial of combination chemotherapy in extensive squamous carcinoma of the lung: A Southwest Oncology Group Study. *Cancer Treat Rep* 1977, **61**, 1623–1629.
26. Randoph VL, Vallejo A, Strong EW, *et al.* Combination treatment with chemotherapy and radiotherapy in head and neck cancer. *Proc Am Assoc Cancer Res and ASCO* 1977, **18**, 336.
27. Kelsen DP, Cvitkovic E, Bains M, *et al. Cis*-dichlorodiammineplatinum (II) and bleomycin in the treatment of esophageal carcinoma. *Cancer Treat Rep* 1978, **62**, 1041–1046.
28. Einhorn LH, Donohue J. *Cis*-diamminedichloroplatinum, vinblastine and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann Intern Med* 1977, **87**, 293–298.
29. Israel L, Breau JL, Aguilera J. Preliminary report of 70% response rate in squamous cell cancer of the lung with a 6 consecutive days combination of cis-platinum bleomycin. *Proc Am Assoc Cancer Res and ASCO* 1981, **22**, 508.
30. Gralla R, Casper E, Kelsen D, Golbey RB. Vindesine and cisplatin combination chemotherapy in non-small cell lung cancer. In: Hansen HH, Dombernowsky P, eds. *Abstracts* II, *World Conference on Lung Cancer Copenhagen.* Amsterdam, Excerpta Medica, 1980, 229.
31. *WHO Handbook for Reporting Results of Cancer Treatment.* Geneva, World Health Organization 1979, WHO Offset Publication No. 48.
32. The World Health Organization histological typing of lung tumours. 2nd edition. *Am J Clin Pathol* 1982, **77**, 123–126.
33. Harmer MH (ed). *TNM Classification of Malignant Tumours.* 3rd edition. Geneva, UICC, 1978.
34. Nelson RL, Dyke RW, Root MA. Clinical pharmacokinetics of vindesine. *Cancer Chemother Pharmacol* 1979, **2**, 243–246.
35. Samuels ML, Holoye PY, Johnson DE. Bleomycin combination chemotherapy in the management of testicular neoplasia. *Cancer* 1975, **36**, 318–326.
36. Cavelli F, Sonntag RW, Jungi F, *et al.* $VP_{16\text{-}213}$ monotherapy for remission induction of small cell lung cancer: a randomized trial using three dosage schedules. *Cancer Treat Rep* 1978, **62**, 473–475.
37. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of nitrogen mustards in the palliative treatment of carcinoma, with particular reference to bronchogenic carcinoma. *Cancer* 1948, **1**, 634–656.
38. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958, **53**, 457–481.
39. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
40. Itri LM, Gralla RJ, Kelsen DP, *et al.* Cisplatin, vindesine and bleomycin (CVB) combination chemotherapy of advanced non-small cell lung cancer. *Cancer* 1983, **51**, 1050–1055.
41. Aisner J, Hansen HH. Commentary: current status of chemotherapy for non-small cell lung cancer. *Cancer Treat Rep* 1981, **65**, 979–986.
42. Stanley KE. Prognostic factors for survival in patients with inoperable lung cancer. *J Natl Cancer Inst* 1980, **65**, 25–32.
43. Woods RL, Levi JA, Page J, *et al.* Non-small cell cancer: a randomised comparison of chemotherapy with no chemotherapy. *Proc Am Soc Clin Oncol* 1985, **4**, 177 (abstract C-691).
44. Woods RL, Levi JA, Page J, *et al.* Non-small cell lung cancer: a randomised comparison of chemotherapy with no chemotherapy. *4th World Conference on Lung Cancer,* Toronto, 1985 (abstract 537).
45. Morrow GR. The assessment of nausea and vomiting: past problems, current issues, and suggestions for future research. *Cancer* 1984, **53** (suppl), 2267–2278.
46. Lewis BM, Izbicky R. Routine pulmonary function tests during bleomycin therapy. *JAMA* 1980, **243**, 347–351.
47. Rudnick SA, Feinestein AR. An analysis of the reporting of results in lung cancer drug trials. *J Natl Cancer Inst* 1980, **64**, 1337–1343.

48. Aaronson NK, Bakker W, Stewart AL, *et al.* A multi-dimensional approach to the measurement of quality of life in lung cancer clinical trials: a joint project of the EORTC Lung Cancer Cooperative Group and the Study Group on Quality of Life. In: Aaronson NK, Beckmann J, Bernheim J, Zettoun R, eds. *Quality of Life in Cancer.* EORTC Monograph Series, New York, Raven Press, 1986 (in press).
49. Presant CA. Quality of life in cancer patients: who measures what? *Am J Clin Oncol* 1984, **7**, 571–573.
50. Simes RJ. Risk–benefit relationships in cancer clinical trials: the ECOG experience in non-small cell lung cancer. *J Clin Oncol* 1985, **3**, 462–472.