Eur J Cancer Clin Oncol, Vol. 23, No. 11, pp. 1615–1619, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00

A Randomized Trial Comparing Vindesine and Cisplatinum to Vindesine and Methotrexate in Advanced Non Small Cell Lung Carcinoma

V.J. HARVEY, M.L. SLEVIN, S.P. CHEEK, M.J. BARNETT, W. GREGORY, J.P.S. THOMPSON and P.F.M. WRIGLEY

ICRF Department of Medical Oncology, St Bartholmew's and Homerton Hospitals, London, U.K.

Abstract—*Combination chemotherapy using vindesine and cisplatinum has been reported to be active in non-small cell lung carcinoma (NSCLC). In an attempt to reduce the potential neurotoxicity of this combination, and to assess the role of cisplatinum, a randomized trial has compared vindesine and cisplatinum to vindesine and methotrexate in* 48 *patients with advanced symptomatic NSCLC. Patient characteristics were similar in the two treatment arms. Objective tumour response and survival were similar for both treatments. No complete response occurred. Four patients receiving vindesine/cisplatinum* (16%) *and three patients receiving vindesine/methotrexate* (13%) *had a partial response. All responses occurred in patients with a performance status of* 70% *or more and no response was seen in patients with squamous cell carcinoma. Median survival for both regimens was* 16 *weeks. Toxicity was considerable and only six patients* (12.5%) *felt better on treatment. Nausea and vomiting were more frequent in the vindesine/cisplatinum arm, but mild neurotoxicity was more common in the vindesine/methotrexate arm. The low response rates, short survival and significant toxicity suggest that the role of combination chemotherapy in NSCLC remains to be established.*

INTRODUCTION

THE SURVIVAL of patients with non small cell lung carcinoma (NSCLC) is poor [1]. Surgery remains the treatment of choice for early stage disease, but is applicable only to a minority of patients [1, 2]. More than half the patients who have surgery with curative intent will relapse, because of metastatic disease occult at the time of operation [1, 2]. Radical radiotherapy has failed to improve these results [3]. The majority of patients with NSCLC could thus potentially benefit from effective systemic therapy. Unfortunately NSCLC is largely resistant to cytotoxic chemotherapy [1, 4–6].

Recently the combination of vindesine and cisplatinum has been reported to have significant activity in this disease [7–11]. Both vindesine and cisplatinum are neurotoxic and cisplatinum is associated with severe and prolonged nausea and vomiting [12]. A recent study comparing vindesine alone to vindesine and high dose cisplatinum or vindesine and cisplatinum and mitomycin C showed that vindesine alone was as good as the combination [13]. Methotrexate is a drug with modest activity in NSCLC [1, 4, 5], which is considerably less toxic than cisplatinum. It seemed likely that the toxicity of therapy might be reduced by combining vindesine with methotrexate rather than cisplatinum. A randomized trial comparing vindesine and methotrexate with vindesine and cisplatinum has been conducted to assess the activity and toxicities of these two regimens and to evaluate the role of cisplatinum in the combination.

Accepted 15 May 1987.

MATERIALS AND METHODS

Patients

Forty-eight consecutive patients with symptomatic inoperable NSCLC were randomized after giving informed consent. All patients had histologically or cytologically confirmed NSCLC with measurable or evaluable disease not amenable to surgery. No patient had had previous chemotherapy. Patient characteristics are shown in Table 1. Performance status was assessed on the Karnofsky scale [14] and staging according to the TNM classification [15].

Treatment

All patients received vindesine according to the

Table 1. Patient characteristics

	Vindesine and cisplatinum	Vindesine and methotrexate
Total	25	23
Male	19	18
Female	6	5
Performance status		
Karnofksy scale [14]		
80–90	11	13
60–70	12	6
≤ 50	2	4
Histology		
(a) Tumour type		
Squamous cell	11	10
Adenocarcinoma	8	10
Large cell	6	3
(b) Tumour grade		
Well differentiated	3	2
Moderately differentiated	6	6
Poorly differentiated	10	11
Undifferentiated	3	3
Unknown*	3	1
TNM stage		
III M0	4	6
III M1	21	17
Previous treatment		
Surgery	2	3
Radiotherapy	5	0

*In four patients with tumour diagnosed by cytology grading could not be determined.

dose schedule used by Gralla *et al.* [7] (3 mg/m^2 weekly × 7 doses and 2 weekly thereafter) and were randomized to either cisplatin 60 mg/m^2 (with mannitol diuresis) or methotrexate 200 mg/m^2 (followed by folinic acid 15 mg po 6 hourly × 12, starting 24 h after methotrexate administration). Cisplatinum and methotrexate were both given intravenously on day 1 of each 28 day cycle. Therapy was continued for a maximum of six cycles for those patients showing an objective response but was discontinued at disease progression or after three cycles in those with static disease.

Assessment of response and toxicity

Standard WHO criteria were used to define objective response and toxicity [16]. Response had to be documented on two separate occasions at least 1 month apart but progressive disease required documentation on only a single occasion.

Subjective response was assessed at each visit. Following detailed assessment of the toxicity of the previous course of chemotherapy patients were asked to categorize their overall feeling of well-being relative to the start of treatment. Categories were much better, somewhat better, the same, somewhat worse and much worse. The two categories of 'better' and of 'worse' were summated for presentation. All assessments while on therapy were combined for the overall results. In practice these were consistently better, the same or worse for a given patient.

Survival

Survival was calculated from date of first treatment on protocol, the survival curves were developed by standard life table analysis [17] and tests of significance by the log-rank method [18]. The analysis was carried out after all patients had died and the curves therefore represent actual rather than actuarial survival.

RESULTS

Response

There was no complete response. Four out of 25 (16%, 95% confidence limits 4–36%) of patients receiving vindesine and cisplatinum showed a partial response as compared to three out of 23 (13%, 95% confidence limits 3–34%) receiving vindesine and methotrexate. No response was seen in the patients with squamous cell carcinoma. Of the four patients receiving vindesine and cisplatinum who achieved a partial response, two had undifferentiated large cell carcinoma and two adenocarcinoma. All three patients achieving a response to vindesine and methotrexate had adenocarcinoma. All responses occurred in patients with a performance status of 70% or greater.

Subjective response was assessed in 45 patients. Six patients felt better (including two with objective partial responses), seven patients were subjectively unchanged (including one objective partial response) and the remaining 32 patients felt worse (including four objective partial responses).

Survival

Median survival was identical for both treatment regimens at 16 weeks (Table 2). At 1 year there was only one survivor in the vindesine and cisplatinum arm compared to six in the vindesine and methotrexate arm ($P = 0.25$) (Fig. 1). There was a trend towards improved survival in patients showing an objective response ($P = 0.08$), and survival was related to both performance status ($P < 0.001$) and subjective response ($P = 0.03$) as shown in Table 2.

Toxicity

Nausea and vomiting were the most prominent side effects and were more common in the vindesine/platinum arm (Table 3). Other side effects were evenly distributed between the two arms with the exception of mild neuropathy (grade 1) which surprisingly occurred more often in the vindesine/methotrexate arm. Renal dysfunction was uncom-

Table 2. Patient survival

	Median survival (weeks)	Patients alive at 1 year (%)	
Vindesine and methotrexate	16	6(26)	$P = 0.25$
Vindesine and cisplatinum	16	1(4)	
Overall responders	39	2(29)	$P = 0.08$
Overall non-responders	14	5(12)	
Performance status			
80–90	24	5(21)	
60–70	14	2(11)	$P < 0.001$
≤ 50	6	0	
Subjective response			
Better	52	3(50)	
Unchanged	22	1(14)	$P = 0.03$
Worse	14	3(9)	

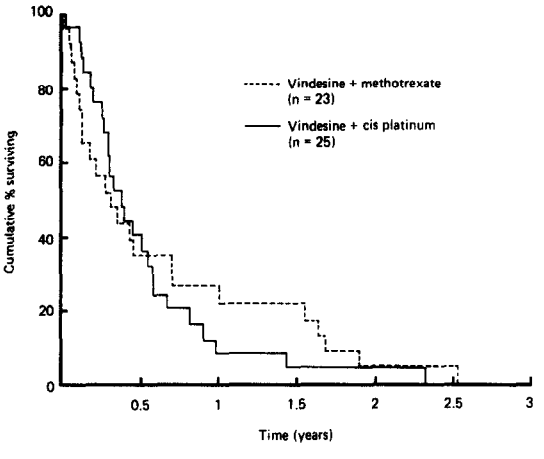

Fig. 1. Patient survival from date of first treatment.

Table 3. Toxicity of therapy

	Vindesine and cisplatinum (% of evaluated patients)	Vindesine and methotrexate (% of evaluated patients)
Nausea		
None/mild (grade 0,1)	25	64
Moderate/severe (grade 2,3)	75	36
Vomiting		
None/mild (grade 0,1)	50	71
Moderate/severe (grade 2,3)	50	29
Mucositis		
None	86	94
Mild (grade 1)	14	6
Alopecia		
None	71	75
Noticeable (grade 2)	29	25
Neuropathy		
None	76	47
Mild (grade 1)	18	40
Moderate (grade 2)	6	13
Renal		
None	82	100
Mild (grade 1)	18	—

mon but occurred to a mild degree (grade 1) in 18% of the patients receiving vindesine and platinum. Alopecia occurred equally in both arms in a quarter of the patients. Mucositis was uncommon.

DISCUSSION

The response rates of 13% and 16% in the two arms of this study were disappointing. Survival was poor with 62% of patients having died within 6 months and 85% having died within 1 year of starting treatment. The toxicity was considerable, especially for the vindesine/cisplatinum arm and few patients experienced a subjective improvement. Indeed several patients felt worse despite an objective partial response. While the assessment of subjective response was simplistic, the results of repetitive testing were consistent in each patient. Subjective deterioration despite objective response has been noted by other workers using a similar regimen [19].

Both vindesine [8, 20–25] and cisplatinum [26–28] have shown activity in NSCLC when used alone. Several studies of vindesine have shown response rates of 25–35% in previously untreated patients, although lower rates (10–15%) have been found following prior treatment [20–22]. Other workers have found low response rates (< 15%) even in untreated patients [7, 23–25]. Cisplatinum used alone gave a response rate of 26% in an EORTC study of 61 patients [26] and 33% in a smaller study of 30 patients [27]. A more modest response rate of only 10% was found in the largest study involving 181 patients [28]. The dose of cisplatinum in this last study (50 mg/m^2) was less than that in the EORTC study (120 mg/m^2) [26]

and that of Vogl *et al.* (75 mg/^{2}) [27] which may have contributed to the lower response rate.

Several workers have reported higher response rates with a combination of cisplatinum and vindesine [7–11, 29]. Gralla *et al.* [7] reported on a randomized trial comparing a regimen identical to the vindesine-cisplatinum arm used in the current study to a regimen using a higher dose cisplatin (120 mg/m^2). The response rate was similar in the two arms of the study (40% for higher dose, 46% for lower dose) but the high dose cisplatinum regimen was associated with a superior median duration of response (12 vs. 5.5 months) and median survival for responding patients (22 vs.10 months). In a randomized study comparing cisplatinum (100 mg/m^2) and vindesine to vindesine alone, Elliot *et al.* [8] reported a response rate of 33% for the combination with a median survival of 11 months compared to a response rate of 7% and a median survival of 4 months for those treated with the single drug. Response rates ranging from 24–83% have been reported for the combination of vindesine and cisplatinum [29] but in the majority of studies response rates between 30–40% and median survival 6–9 months have been achieved [9–11]. The dosage of platinum in most regimens has been 100–120 mg/m^2 [7–11, 29], only the low dose arm of Gralla *et al.* [7] (60 mg/m^2) and the study of Holsti *et al.* [30] (90 mg/m^2; response rate 83%) employing lower doses. Although these regimens with lower doses of platinum were associated with equivalent response rates, the dose of platinum in the current study (60 mg/m^2) may have contributed to the lesser response rate and short survival.

An alternative explanation for the poor results obtained in this paper is the policy of treating only patients with significant symptomatic disease which may have led to the selection of a group of patient with more advanced disease and a poorer prognosis. Despite this policy the majority of patients had a good performance status (Table 1).

It is of interest that there was no response in patient with squamous cell carcinoma. A similar finding was noted into two early studies of vindesine [23, 24], but not in many others.

Few patients were improved subjectively by treatment. In the vindesine/cisplatinum arm, only one patient felt better on treatment while five patients improved (subjectively) in the vindesine/methotrexate arm. The vast majority of patients (20 in the vindesine/cisplatinum arm and 13 in the vindesine/methotrexate arm) showed subjective deterioration on treatment. The failure of the majority of objective responders to feel better is unusual and suggests that the toxicity of therapy substantially interfered with the patient's quality of life. Although a higher dose of cisplatinum might have improved the objective response rate, it is likely that this would have increased further the toxicity of this regimen.

Despite the many studies using vindesine/cisplatinum combinations in NSCLC the benefit to patients of such treatment remains uncertain [1]. In a preliminary report of a randomized trial comparing vindesine/platinum chemotherapy with no chemotherapy, Woods *et al.* [31] found an objective response rate to chemotherapy of 30%, but no difference in survival and significant toxicity from therapy. The data in the current study have shown low response rates to both chemotherapy regimens, with short survival and significant toxicity. This has emphasized the unproven role of chemotherapy in NSCLC. Future studies should compare therapy to untreated controls.

REFERENCES

1. Minna JD, Higgins GA, Glatstein EJ. Cancer of the lung. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*, 2nd Edn. Philadelphia, JB Lippincott, 1985, 507–597.
2. Mountain CF. Therapy of stage I and stage II non-small cell lung cancer. *Semin Oncol* 1983, **10**, 71–80.
3. Cox JD, Byhardt RW, Komaki R. The role of radiotherapy in squamous, large cell and adenocarcinoma of the lung. *Semin Oncol* 1983, **10**, 81–94.
4. Hoffman PC, Bitran JD, Golomb HM. Chemotherapy of metastatic non-small cell bronchogenic carcinoma. *Semin Oncol* 1983, **10**, 111–122.
5. Bakowski MT, Crouch JC. Chemotherapy of non-small cell lung cancer: a reappraisal and a look into the future. *Cancer Treat Rev* 1983, **10**, 159–172.
6. Muggia FM, Blum RH, Foreman JD. The role of chemotherapy in the treatment of lung cancer: evolving strategies for non-small cell histologies. *Int J Radiat Oncol Biol Phys* 1984, **10**, 137–145.
7. Gralla RJ, Casper ES, Kelsen DP *et al.* Cisplatin and vindesine combination chemotherapy for advanced carcinoma of the lung: a randomised trial investigating two dosage schedules. *Ann Intern Med* 1981, **95**, 14–420.
8. Elliott 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 randomised study. *Eur J Cancer Clin Oncol* 1984, **20**, 1025–1032.
9. Dhingra HM, Valdivieso M, Carr DT *et al.* Randomised trial of three combinations of cisplatin with vindesine and/or VP-16-213 in the treatment of advanced non-small-cell

lung cancer. *J Clin Oncol* 1985, **3**, 176–183.
10. Carmichael J, Gregor A, Cornbleet MA *et al.* *Cis*-platinum and vindesine in combination in the treatment of non-small cell lung cancer. *Eur J Cancer Clin Oncol* 1985, **21**, 811–814.
11. Kris MG, Gralla RJ, Kalman LA *et al.* Randomised trial comparing vindesine plus cisplatin with vinblastine plus cisplatin in patients with non-small cell lung cancer, with an analysis of methods of response assessment. *Cancer Treat Rep* 1985, **69**, 387–395.
12. Dorr RT, Fritz WL, eds. *Cancer Chemotherapy Handbook*. New York, Elsevier North Holland, 1980, 315–323, 692–698.
13. Einhorn LH, Loehrer PJ, Williams SD *et al.* Random prospective study of vindesine versus vindesine plus high-dose cisplatin versus vindesine plus cisplatin plus mitomycin C in advanced non-small-cell lung cancer. *J Clin Oncol* 1986, **4**, 1037–1043.
14. Karnofsky DA, Abelman WH, Craver LF, Burchenal JH. The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer* 1948, **1**, 634–656.
15. Harmer MH, ed. *TNM Classification of Malignant Tumours*, 3rd Edn. Geneva, UICC, 1978, 41–45.
16. Miller Ab, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
17. Armitage P. *Statistical Methods in Medical Research*. London, Halstead Press, 1971.
18. Peto R, Pike MC, Armitage P *et al.* Design and analysis of randomised clinical trial requiring prolonged observation of each patient. II Analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
19. Esseesse I, Platica O, Chandra P, Rothenberg SP. Poor response and impaired quality of life of patients with non-small cell lung cancer treated with vinblastine and *cis*-platinum. A follow-up report. *Proc Am Soc Clin Oncol* 1986, **5**, 170. (Abstract 667)
20. 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.
21. 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.
22. Luedke SL, Luedke DW, Petruska P, Broun GO, Reed G, Leavitt J. Vindesine (VDS) monochemotherapy for non-small cell lung cancer: a report of 45 cases. *Cancer Treat Rep* 1982, **66**, 1409–1411.
23. Osterlind K, Horbov S, Dombernowsky P, Rorth 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.
24. Mattson K, Holsti LR, Salmo M, Saastamoinen M, Ahlstedt S, Holsti P. Vindesine in the treatment of small cell and non-small cell bronchogenic carcinoma: preliminary results. *Cancer Treat Rev* 1980, **7** (Suppl), 65–70.
25. Jewkes J, Harper PG, Tobias JS, Geddes DM, Souhami RL, Spiro SG. Comparison of vincristine and vindesine in the treatment of inoperable non-small cell bronchial carcinoma. *Cancer Treat Rep* 1983, **67**, 1119–1121.
26. De Jaeger R, Longeval E, Klastersky J. High-dose cisplatin with fluid and mannitol-induced diureses in advanced lung cancer: a phase II clinical trial of the EORTC Lung Cancer Working Party (Belgium). *Cancer Treat Rep* 1980, **64**, 1341–1346.
27. Vogl SE, Berenzweig M, Camacho F, Greenwald E, Kaplan BH. Efficacy study of intensive cisplatinum therapy in advanced non-small cell bronchogenic carcinoma. *Cancer* 1982, **50**, 24–26.
28. Panettiere FJ, Vance RB, Stuckey WJ, Coltman CA, Costanzi JJ, Chen TT. Evaluation of single-agent cisplatin in the management of non-small call carcinoma of the lung: a Southwest Oncology Group Study. *Cancer Treat Rep* 1983, **67**, 399–400.
29. Sculier JP, Klastersky J. Progress in chemotherapy of non-small cell lung cancer. *Eur J Cancer Clin Oncol* 1984, **20**, 1329–1333.
30. Holsti LR, Mattson K, Grohn P *et al.* Cisplatinum plus vindesine versus CDDP and VP-16 in combination with radiotherapy in the treatment of non-small cell carcinoma of the lung (abstract). Abstracts of the IIIrd World Conference on Lung Cancer, Tokyo, 1982, 274.
31. Woods RL, Levi JA, Page J *et al.* Non-small cell cancer: a randomised comparison of chemotherapy with no chemotherapy (Abstract C-691). *Proc Am Soc Clin Oncol* 1985, **4**, 177.