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Cisplatin, vinblastine, and bleomycin in inoperable non-small cell lung cancer

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ABSTRACT Forty two patients with inoperable non-small cell lung cancer were entered into a phase II study of the combination chemotherapy regimen PVB (cisplatin 60 mg/m^2 by intravenous infusion over two hours on day 1, vinblastine 4 mg/m^2 by intravenous bolus on days 1 and 2, and bleomycin 15 mg intramuscularly on days 1, 8, and 15), repeated at three weekly intervals. Twelve of 40 evaluable patients (30%) achieved partial responses; there were no complete responses. The median duration of response was 16 weeks (range >8–73 weeks). The median survival of responding patients calculated from entry to the study until death (40 weeks) was superior to that of patients failing to respond (15 weeks). Treatment was accompanied by signs of moderate toxicity, particularly myelosuppression, nausea and vomiting, alopecia, and neuropathy. One patient died from a neutropenic infection. PVB is a moderately toxic regimen for non-small cell lung cancer and appears similar in efficacy and toxicity to high dose cisplatin and vindesine.

The results of chemotherapy in the treatment of non-small cell lung cancer have been disappointing, especially when compared with the high response rates and prolongation of survival which chemotherapy may produce in the treatment of small cell lung cancer.[1,2] Most single agents active against non-small cell lung cancer induce response in less than 20% of patients[3,4] and combination chemotherapy has led to little improvement in response rates or survival.[5–8] Cisplatin in one of the more active single agents, producing a cumulative response rate of 19% from published series.[9–13] The combination of vindesine with cisplatin appears to increase the response rate[14,15] and one study noted that the median survival for responding patients receiving high dose cisplatin and vindesine was 22 months.[15] Recent attempts to improve the response rate to cisplatin and vindesine by including more drugs in the combination have not, however, proved rewarding.[16,17]

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Cisplatin has been combined with another vinca alkaloid, vinblastine, producing a response rate similar to that for cisplatin with vindesine.[18,19] At the start of this study, the combination of cisplatin, vinblastine and bleomycin (PVB) had been reported to be highly successful in the treatment of germ cell tumours[20] and it was reported subsequently to be of use in the treatment of adenocarcinoma of unknown primary site.[21] Furthermore, phase II studies with PVB had been initiated in our institutes for cervical cancer and head and neck cancer, and these showed the activity of this regimen.[22] We decided therefore to investigate the role of PVB in the management of inoperable non-small cell lung cancer.

Methods

PATIENTS

From October 1979 to May 1983, 42 patients with inoperable non-small cell lung cancer, from two institutions, were entered into the study after informed consent had been obtained. Thirty three were male and nine female; the median age was 56 years (range 41–74 years). All had a performance status of 2 or better on the ECOG scale.[23] Histological examination showed large cell undifferen-

tiated carcinoma in 19, adenocarcinoma in 11, and squamous carcinoma in 12. Seventeen patients were staged as having limited disease (disease restricted to one hemithorax with or without ipsilateral supraclavicular lymph nodes affected) and 25 as having extensive disease (disease outside these limits). Seventeen had received no prior treatment, but 24 had received radiotherapy and three had undergone surgery. None had received prior chemotherapy. Fifteen patients reported no weight loss at entry to the study, 11 a weight loss of 5% or less, and 16 patients a weight loss of more than 5% in the six months before entry to the study.

Drug treatment

Treatment consisted of cisplatin 60 mg/m^2 by intravenous infusion over two hours on day 1, vinblastine 4 mg/m^2 by intravenous bolus on days 1 and 2, and bleomycin 15 mg by intramuscular injection each week. Treatment was repeated at three weekly intervals. For responding patients the programme was continued for two courses beyond the maximal response, provided that a cumulative dose of 300 mg of bleomycin was not exceeded. Patients with stable or progressive disease stopped treatment after a minimum of six weeks. Treatment was deferred by one week if the platelet count was under 100 × 10^9/l or the white blood count was under 3 × 10^9/l when the next cycle was due. If the blood count remained below these limits after one week, the subsequent dose of vinblastine was halved or the next cycle omitted, according to the degree of myelosuppression. Similarly, the bleomycin dosage was halved or bleomycin withdrawn if carbon monoxide transfer (TLCO) fell by 10% or more below the pretreatment value or to less than 65% of the predicted normal level at any time during treatment. Cisplatin was reduced in dosage or withdrawn if there was evidence of deterioration in renal function (a rise in serum creatinine greater than 20 μmol/l) (0.23 mg/100 ml). Antiemetic medication was prescribed only if patients experienced nausea or vomiting accompanying treatment.

Assessment of response and toxicity

Response was classified according to standard criteria.[24] Briefly, a complete response meant the disappearance of all primary and metastatic disease and a partial response a 50% or greater reduction in measurable or evaluable tumour, both for a minimum of six weeks. Progressive disease meant a 25% increase in size of at least one measurable lesion or the appearance of new lesions. Patients with changes outside these limits nine weeks or more after the start of treatment were classified as having stable disease. The duration of response was defined as the period of time between entry to the study and the first observation of disease progression.

Patients were considered evaluable for response if they had received a minimum of two cycles of treatment, or if treatment was abandoned after one cycle because of rapid disease progression. Response and toxicity were assessed at each cycle by clinical evaluation and investigations including chest radiography (posteroanterior and lateral), a full blood count, and a standard biochemical screen. Full blood counts were not, however, carried out between courses. Special investigations such as bone radiography, computed tomography, and radioisotope or ultrasound scanning were carried out where indicated. Toxicity was graded according to standard

Table 1 *Response in relation to prognostic factors at entry to the study*

	No	*CR*	*PR*	*SD*	*PD*	*CR + PR (%)*
All patients	40	0	12	17	11	30
ECOG performance status[23]						
0	9	0	3	5	1	33
1	14	0	6	5	3	43
2	17	0	3	7	7	18
Weight loss						
None	14	0	7	5	2	50
<5%	10	0	4	3	3	40
>5%	16	0	1	9	6	6
Extent of disease						
Limited	17	0	4	6	7	24
Extensive	23	0	8	11	4	35
Histology						
Large cell undifferentiated carcinoma	19	0	4	7	8	21
Squamous cell carcinoma	11	0	5	5	1	45
Adenocarcinoma	10	0	3	5	2	30
Radiotherapy						
Prior radiotherapy	24	0	6	11	7	25
No prior radiotherapy	16	0	6	6	4	38

CR—complete response; PR—partial response; SD—stable disease; PD—progressive disease.

World Health Organisation criteria.[25]

Results

OBJECTIVE RESPONSE

Two patients were regarded as not evaluable for response as they had received only one course of treatment without obvious disease progression; one was lost to follow up and one refused further treatment. Of the remaining 40 patients, partial responses were observed in 12 (30%). No complete responses occurred. Responders achieved a response after a mean of 1.8 courses of treatment (range 1–4 courses). The median duration of response was at least 16 weeks (range >8–73 weeks). There were three early deaths, after the first course; all these patients were included and classed as having disease progression. Eleven patients in all were classified as having progressive disease. Seventeen patients were classified as having stable disease after a mean of 3.8 courses (range 2–10 courses).

Response rates according to histological classification, ECOG performance score, weight loss, and extent of disease are shown in table 1. The only factors associated with an increased likelihood of response appeared to be having no prior weight loss, no prior radiotherapy, and possibly a diagnosis of squamous cell carcinoma.

SURVIVAL

Life table analysis using the Breslow version of the generalised Wilcoxon test[26] showed that the median survival of responders calculated from entry to the study until death was superior to that of non-responders (40 weeks *v* 15 weeks; $p < 0.01$).

Table 2 *Toxicity of the cisplatin, vinblastine, and bleomycin regimen in 40 patients with non-small cell lung cancer*

	No (%) of patients
Leucopenia*	22 (55)
Thrombocytopenia*	1 (3)
Infection	3 (8)
Nausea	11 (27)
Vomiting	29 (73)
Mild alopecia	13 (33)
Moderate or severe alopecia	13 (33)
Stomatitis	6 (15)
Diarrhoea	4 (10)
Constipation	4 (10)
Peripheral neuropathy	4 (10)
Skin changes	2 (5)
Cystitis	2 (5)
Fever	1 (3)
Phlebitis	1 (3)
Neutropenic death	1 (3)

*Based on blood counts at time of retreatment.

TOXICITY

Forty of 42 patients were evaluable for toxicity. Myelosuppression and nausea and vomiting were the most serious manifestations of toxicity encountered during the study. Although weekly blood counts were not performed, leucopenia was noted in 22 of the 40 patients. Two patients developed neutropenic infections, and one of these died despite intravenous antibiotics. A further patient required oral antibiotic treatment. Thrombocytopenia was noted in one patient.

All patients experienced appreciable gastrointestinal side effects; in 11 patients only nausea occurred during treatment, but in the remaining 29 this was accompanied by vomiting. In 24 patients vomiting was transient, while five experienced persistent vomiting that responded poorly to antiemetic medication. Diarrhoea was noted in four patients and constipation in four. Mild alopecia occurred in 13 and patchy alopecia in 11 but only two patients required wigs. Peripheral neuropathy developed in four patients.

Deterioration in pulmonary function necessitated bleomycin withdrawal in one patient after 225 mg, while two further patients developed skin changes typical of bleomycin toxicity. Two patients required reduction of the cisplatin dose because of transient renal impairment in one and peripheral neuropathy in the other. The occurrence of toxicity encountered during the study is summarised in table 2.

Discussion

Our study shows that the combination of cisplatin, vinblastine, and bleomycin caused tumour regression in 30% of patients with non-small cell lung cancer. Although there have been no previous reports of PVB as treatment for non-small cell lung cancer, vindesine combined with cisplatin and bleomycin has recently been reported to induce tumour regression in 20 of 52 (38%) of such patients, previously untreated.[27] The authors noted that the median survival for responders was 64 weeks compared with only 20 weeks for non-responders ($p < 0.001$) and concluded that the results of this triple agent regimen were similar to those obtained previously with high dose cisplatin and vindesine. In a further study, using cisplatin, vinblastine, and mitomycin C, responses were observed in 12 of 26 patients (46%), with a median duration of response of 26 weeks[28]; but the authors again concluded that the addition of mitomycin C did not improve the results obtained with cisplatin and a vinca alkaloid. Together these studies suggest that cisplatin and the vinca alkaloid are the important components of the combinations evaluated.[29] In

our experience with the PVB regimen, treatment was accompanied by frequent and often severe toxicity and the survival benefit for responders was only six months—somewhat less than that reported in patients receiving high dose cisplatin and vindesine.[15]

Aisner and Hansen emphasised the importance of low performance capacity, extensive disease, and prior weight loss as adverse prognostic factors in the treatment of non-small cell lung cancer.[30] In the present study performance score and extent of disease were not important prognostic factors influencing outcome, although no prior weight loss, no prior radiotherapy, and possibly the presence of the squamous cell type appeared to be associated with an increased likelihood of response to treatment and increased survival. The small numbers in each subgroup do not, however, allow firm conclusions to be drawn.

In any trial of palliative chemotherapy in advanced malignant disease it is important to weigh the benefits of treatment, such as improvement in symptoms and possibly survival, in responding patients against the toxic effects experienced by all patients. This is particularly important for non-small cell lung cancer, where response rates are usually relatively low and survival is short. Only two series have so far been reported in which chemotherapy has been compared with placebo in patients with non-small cell lung cancer.[31 32] Although the results of both indicated a survival benefit for patients responding to chemotherapy this might reflect the better performance status of patients subsequently achieving a response, and further randomised studies of chemotherapy versus no chemotherapy in the management of non-small cell lung cancer will be necessary to establish clearly which subgroups of these patients may benefit from chemotherapy.

Meanwhile the conclusion is that platinum based combination chemotherapy is a toxic form of treatment which causes tumour regression or palliation in only about one third of patients.

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References

1 Aisner J, Alberto P, Bitran J, *et al.* Role of chemotherapy in small cell lung cancer: a consensus report of the International Association for the Study of Lung Cancer Workshop. *Cancer Treat Rep* 1983; **67**:37–43.
2 Comis RL. Small cell carcinoma of the lung. *Cancer Treat Rev* 1982;**9**:237–58.
3 Bakowski MT, Crouch JC. Chemotherapy of non-small cell lung cancer: a reappraisal and a look to the future. *Cancer Treat Rev* 1983;**10**:159–72.
4 Hoffman PC, Bitran JD, Golomb HM. Chemotherapy of metastatic non-small cell bronchogenic carcinoma. *Semin Oncol* 1983;**10**:111–22.
5 Edmonson JH, Lagakos SW, Selawry OS, *et al.* Cyclophosphamide and CCNU in the treatment of inoperable small cell carcinoma and adenocarcinoma of the lung. *Cancer Treat Rep* 1976;**60**:925–32.
6 Eagan RT, Carr DT, Coles DT, Rubin J, Frytak S. ICRF-159 versus polychemotherapy in non-small cell lung cancer. *Cancer Treat Rep* 1976;**60**:947–51.
7 Bodey GP, Lagakos SW, Gutierrez AC, Wilson HE, Selawry OS. Therapy of advanced squamous carcinoma of the lung: cyclophosphamide versus "COMB." *Cancer* 1977;**39**:1026–31.
8 Davis S, Pandya MR, Rambotti P. Single-agent and combination chemotherapy for extensive non-small cell carcinoma of the lung. *Cancer Treat Rep* 1980;**64**:685–8.
9 Rossof AH, Bearden JD, Coltman CA. Phase II evaluation of cis-diamminedichloroplatinum (II) in lung cancer. *Cancer Treat Rep* 1976;**60**:1679–80.
10 Britell JC, Eagan RT, Ingle JN, Creagan ET, Rubin J, Frytak S. Cis-dichlorodiammineplatinum (II) alone followed by adriamycin plus cyclophosphamide at progression versus cis-dichlorodiammineplatinum (II), adriamycin, and cyclophosphamide in combination for adenocarcinoma of the lung. *Cancer Treat Rep* 1978;**62**:1207–10.
11 Casper ES, Gralla RJ, Kelsen DP, Cvitkovic E, Golbey RB. Phase II study of high dose cis-dichlorodiammineplatinum (II) in the treatment of non-small cell lung cancer. *Cancer Rep* 1979; **63**:2107–9.
12 Berenzweig M, Vogl SE, Kaplan BH, Landham R. Phase II trial of cis-diamminedichloroplatinum in patients with non-small cell bronchogenic carcinoma not exposed to prior chemotherapy. *Proc Am Soc Clin Oncol* 1980;**21**:457.
13 DeJager R, Libert P, Michel J, Mairesse P, Thiriaux M. Phase II clinical trials with high dose cisplatin with mannitol induced diuresis in advanced bronchogenic cancer. *Proc Am Soc Clin Oncol* 1980;**21**:363.
14 Elliott JA, Ahmedzai S, Stevenson RD, Dorward AJ, Calman KC. Randomized comparison of vindesine (VDS) versus vindesine plus cis-platinum (DDP) in inoperable non-small cell lung cancer (NSCLC). In: *Proceedings of Third World Conference on Lung Cancer.* Tokyo, 1982:278 (abstract).
15 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**:414–20.
16 Kelsen DP, Gralla R, Stoopler M, *et al.* Cisplatin, doxorubicin, cyclophosphamide and vindesine combination chemotherapy for non-small cell lung cancer. *Cancer Treat Rep* 1982;**66**:247–51.
17 Klastersky J, Nicaise C, Longeval E, *et al.* Cisplatin and etoposide with or without vindesine in non small cell lung cancer. In: Proceedings of Third World Conference on Lung Cancer. Tokyo, 1982:277 (abstract).
18 Stoopler MB, Jaretzki A, Rakowski TJ, Garrett J, Ellison RR. Combination chemotherapy of non-small cell lung cancer with vinblastine and cisplatin. In: Proceed-

ings of Third World Conference on Lung Cancer. Tokyo, 1982:279.
19 Stoopler MB, Jaretzki A, Rakowski TJ, Garrett J, Ellison RR. Vinblastine (VLB) and cis-dichlorodiammineplatinum (DDP) combination chemotherapy in non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1982;**2**:141 (abstract).
20 Einhorn LH, Donohue JP. Cis-diamminedichloroplatinum, vinblastine and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann Intern Med* 1977;**87**:293–8.
21 Woods RL, Milliken ST, Levi JA, *et al.* Comparison of anti-tumour effect and toxicity of combination cisplatinum, vinblastine and bleomycin (PVB) with combination adriamycin and mitomycin C (AM) therapy in metastatic adenocarcinoma of unknown primary site. In: Proceedings of 10th annual scientific meeting, Clinical Oncology Society of Australia. Brisbane: 1983:123 (abstract).
22 Friedlander ML, Kaye SB, Sullivan A, *et al.* Cervical carcinoma: a drug-responsive tumor—experience with combined cisplatin, vinblastine and bleomycin therapy. *Gynecol Oncol* 1983;**16**:275–81.
23 Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Oncol (CTT)* 1982;**5**:649–55.
24 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;**47**:207–14.
25 World Health Organisation. *WHO handbook for reporting results of cancer treatment.* Geneva: WHO, 1979 (Offset Publication, No 48).
26 Dixon WJ, ed. Survival analysis. *BMDP statistical software.* Berkeley: University of California Press, 1981.
27 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**:1050–5.
28 Schulman P, Budman DR, Weiselberg L, Vinciguerra V, Degnan TJ. Phase II trial of mitomycin, vinblastine and cisplatin (MVP) in non-small cell bronchogenic carcinoma. *Cancer Treat Rep* 1983;**67**:943–5.
29 Kalman LA, Kris MG, Gralla RJ, *et al.* Vinca alkaloid and cisplatin combination therapy in non-small cell lung cancer (NSCLC): results of a randomized trial with a comparison of methods of response assessment in 109 patients. *Proc Am Soc Clin Oncol* 1983;**2**:201 (abstract).
30 Aisner J, Hansen H. Current status of chemotherapy for non-small cell lung cancer. *Cancer Treat Rep* 1981;**65**:979–86.
31 Selawry O, Krant M, Scotto J, *et al.* Methotrexate compared with placebo in lung cancer. *Cancer* 1977;**40**:4–8.
32 Cormier Y, Bergeron D, Laforge J, *et al.* Benefits of polychemotherapy in advanced non-small cell bronchogenic carcinoma. *Cancer* 1982;**50**:845–9.