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Cis-platinum and Vindesine in Combination in the Treatment of Non-Small Cell Lung Cancer

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Abstract—*Sixty-three patients with advanced non-small cell carcinoma of the bronchus were treated with a combination of* cis*-platinum and vindesine. All patients had measurable disease and were of good performance status; none had received prior chemotherapy or radiotherapy. Thirty-three per cent of patients responded, with five patients achieving complete remission. Median duration of response was* 4 months, *with a median survival of* 14 months *in the responsers, compared with* 6.5 months *in the whole group and* 4.8 months *in the non-responders. Severe toxicity was encountered, with alopecia, gastrointestinal toxicity and neurotoxicity common. Myelosuppression and renal toxicity were not dose-limiting. Thus the activity of this drug combination is confirmed, but severe toxicity precludes its widespread use in clinical practice.*

INTRODUCTION

PROGNOSIS for patients with non-small cell lung cancer (NSCLS) remains poor. Surgery can be effective in resectable local disease, but less that 10% of all patients with lung cancer survive 3 yr [1].

Radiotherapy offers useful palliation of symptoms but its effect on survival is minimal, with 30-60% 1-yr and <8% 5-yr survival in patients with limited disease treated with a radical dose [2].

As the majority of patients develop disseminated disease, effective systemic therapy could make a significant impact on survival. Whilst small cell carcinoma of the bronchus has been established as a chemosensitive disease with corresponding prolongation of survival [3], NSCLC remains relatively resistant to most cytotoxic drugs. Response rates to single agents have been poor [4], and have been little improved by combination chemotherapy [5]. Recently improved response rates have been reported for combinations of *cis*-platinum (DDP) and vindesine (DVA). Gralla *et al.* [6] reported a 43% response rate to two combinations of these agents, showing an increased duration of response and survival in the group treated with the higher dose of DDP. The incorporation of additional agents into the regimen has not improved response or survival [7, 8].

We have used a combination of DDP and DVA in an attempt to confirm activity, identify possible prognostic factors associated with response and assess treatment-related toxicity.

MATERIALS AND METHODS

Sixty-three patients with histologically proven, inoperable non-small cell carcinoma of the bronchus were treated between March 1981 and May 1983. All patients had evaluable disease, were of good performance status and had received no prior radiotherapy or chemotherapy. They had normal hematological indices and no hepatic or renal disease. All the histology was reviewed by one pathologist (MAM). Patient details are summarised in Table 1. Thirty patients had intrathoracic disese (TNM stages II or III) and 33 patients had metastatic disease, as described in

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Table 2. Patients with cerebral metastases at presentation were not included (five patients subsequently developed evidence of CNS involvement).

Prior to entry into the study all patients had a full clinical examination, chest X-ray, barium swallow, diaphragmatic screening and audiometry. Blood tests included full haematological indices, electrolytes, liver function tests and creatinine clearance. All patients underwent bronchoscopy for diagnosis and staging, even though in some the diagnosis was established by lymph node biopsy; histological details are shown in Table 1. Liver ultrasound and isotope bone scans were only performed when metastatic disease was suspected clinically or because of abnormal biochemical results.

The treatment schedule consisted of DVA 3 mg/m^2 intravenously on days 0, 7, 14 and 21 and DDP 100 mg/m^2 on days 0 and 21, which was infused in 500 ml 10% mannitol over 30 min following 6 hr prehydration with 1 l dextrose/saline. A further 1.5 l dextrose/saline was administered over the next 18 hr. Cycles of chemotherapy were repeated every 42 days. Full haematological and biochemical profiles, and clinical and radiological assessments were carried out prior to each cycle, in addition to an appraisal of treatment-related toxicity. Response was assessed following three courses of treatment unless progressive disease or unacceptable toxicity made earlier cessation of treatment necessary.

Regardless of response, cumulative toxicity precluded chemotherapy beyond three courses. All pretreatment investigations were repeated at this stage except bronchoscopy, which was restricted to patients in whom there was a clinical response. Clinical responses were defined as follows: complete remission (CR) was the disappearance of all evaluable disease including bronchoscopic assessment. and partial remission (PR) was greater than 50% reduction in measurable tumour diameters.

Table 1. Patient details

No. of patients	63
Sex, M:F	43:20
Age (yr)	
Median	58.5
Range	38–70
Performance status (ECOG)	
0	26 (41%)
1	24 (38%)
2	13 (21%)
Cell type	
Squamous carcinoma	43 (68%)
Adenocarcinoma	15 (24%)
Large cell carcinoma	5 (8%)
Disease extent	
Intrathoracic	30 (48%)
Metastatic	33 (52%)

Table 2. Site of metastatic disease

Site	No. of patients
Liver	9
Distal lymphatics*	9
Bone	7
Skin	5
Intrapulmonary	4
Pleural effusion	3

*Including cervical node.

RESULTS

All 63 patients were evaluable for response. The results are outlined in Table 3. The overall response rate was 33%, with five patients (8%) achieving a complete remission, confirmed by bronchoscopy. Similar response rates were noted for all cell types. Patients with limited disease on entry responded significantly better than those with extensive disease (χ^2, $P<0.05$). There was no significant sex difference and performance status on entry into the study had no relationship to response.

Median duration of response was 4 months (range 2–15 months), although two patients remain in remission following observation periods of 6 and 8 months respectively.

Median survival of responding patients was 14 months, compared with 4.8 months for non-responding and 6.5 months in the overall group. Survival curves are shown in Fig. 1. Ten patients

Table 3. Response

Group	No.	CR	PR	OR	%	
All	63	5	16	21	33	
Squamous	43	1	13	14	32	
Adenocarcinoma	15	3	12	15	33	N.S.
Large cell	5	1	1	2	40	
Male	43			13	30	N.S.
Female	20			8	40	
Limited disease	30	3	11	14	47	$P<0.05$
Extensive disease	33	2	5	7	21	
Performance status						
0	26			11	42	
1	24			6	25	N.S.
2	13			4	30	

OR = objective response (CR + PR). N.S. = not significant.

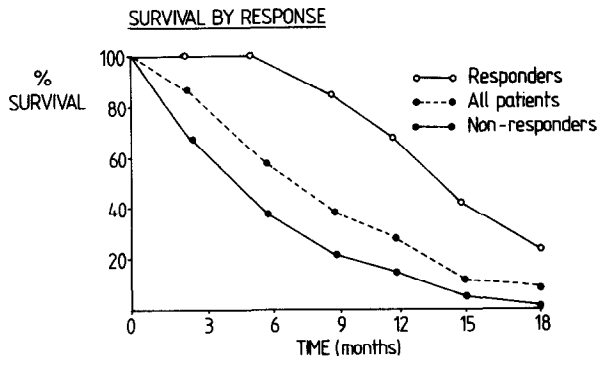

Fig. 1.

remain alive 6-25+ months after entry into the study.

All 63 patients were evaluable for toxicity and the results are listed in Table 4 using WHO criteria. Side-effects were common and often severe. Alopecia was universal and severe gastrointestinal toxicity was frequent, although in 40% vomiting was controlled with high-dose metoclopramide [9]. Haematological toxicity was moderate, mainly causing leucopenia, although blood transfusion was required in 20 patients following at least two cycles of treatment. Peripheral neuropathy was also common, WHO grade 3 in nine patients, but reversible in all cases. High-tone hearing loss was noted on audiometric testing in 16 patients, and was symptomatic in ten cases. Renal impairment was not a clinical problem, but was demonstrated by a decrease in mean creatinine clearance value following treatment to 1.25 ml/sec, compared with a mean pretreatment value of 1.61 ml/sec ($P < 0.0005$, paired t test). Two patients experienced transient decreases in renal function following the first administration of DDP but recovery was prompt and complete; both patients completed their treatment as planned.

Regardless of response, performance status deteriorated in 20 patients following treatment, 39 were unchanged, with improvement in only four cases. Weight loss was marked, with a mean loss of 2.75 kg in responding patients and 4.8 kg in non-responders.

Table 4. *Toxicity (WHO criteria)—63 patients*

Alopecia		
Grade 2/3	63	100%
Gastrointestinal		
Grade 2	15	
Grade 3	39	
Total	54	86%
Neurotoxicity		
Peripheral		
Grade 1	15	24%
Grade 2	15	24%
Grade 2	9	14%
Deafness	16	24%
Constipation	10	16%
Haematological		
WBC		
Grade 2	33	52%
Grade 3	7	11%
RBC		
Grade 2	20	32%

DISCUSSION

Until recently the results of chemotherapy in NSCLC were extremely disappointing. Single agents demonstrated minimal activity and little improvement was seen with combination chemotherapy [5]. One of the best studied regimes was a five-drug combination (BACON) reported by Livingstone in 1976 [10]. Encouraging responses seen initially with this combination were not confirmed when larger numbers of patients were treated, with only a 20% response rate in 116 patients, and with considerable toxicity.

Recently reports by Gralla and co-workers [6-8] have shown response rates of 30-50% with combinations of DVA and DDP. One study compared the effects of low-dose DDP (60 mg/m^2 every 6 weeks) with high-dose (120 mg/m^2 every 4 weeks) when combined with DVA 3 mg/m^2 weekly for 6 weeks, then alternate weekly. Responses were similar in both groups but duration of response was much longer with the high-dose regimen. The other studies using high-dose DDP failed to show any improvement in response with the addition of cyclophosphamide, adriamycin or bleomycin to the regimes.

We report a similar 33% response rate in 63 patients of good performance status. The patients studied included more patients with squamous carcinoma than in Gralla's group, but our results, in agreement with his, show no difference in response rates in different histological categories (Fig. 2).

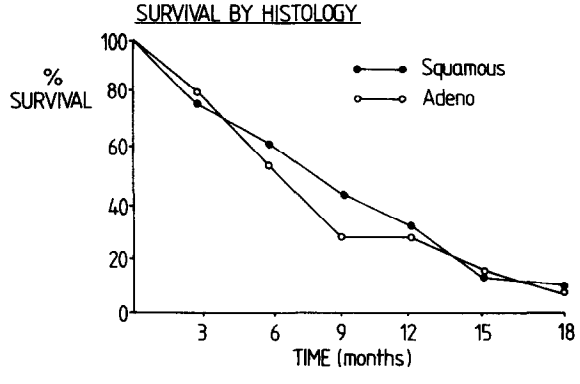

Fig. 2.

In contrast, however, duration of response and survival was disappointingly short in our study compared with those reported by Gralla. Despite a relatively large dose of DDP, 100 mg/m² 3 weekly × 6, the median duration of response was only 4 months. However, treatment was discontinued at 18 weeks, whereas in Gralla's study it was continued until disease progression or unacceptable toxicity supervened. Median survival of the responders in our study was 14 months, with a 1-yr survival of 67%. Non-responders had a median survival of 4.8 months, with a 1-yr survival of 15%. In the whole group of 63 patients the corresponding figures were 6.5 months and 29% respectively.

Toxicity with this regimen was considerable, with deterioration in performance status commonly following treatment. Alopecia and gastrointestinal toxicity were almost universal, the latter being controlled in only 40% with high-dose metoclopramide [9]. Transient diarrhoea in 24% of patients was attributed to DDP therapy, with constipation occurring in 16% following DVA. Weight loss was almost invariable, with a mean loss of 4.1 kg in all patients.

This study confirms the activity of DVA and DDP in combination in the treatment of non-small cell carcinoma of the bronchus. However, we are unable to judge the effect of this therapy on the duration of survival of patients with these cancers. The brief response duration and toxicity of this therapy demands a controlled trial including an untreated group to fully evaluate its role in the management of non-small cell lung cancer.

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