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Vindesine and Cisplatin Combination Chemotherapy Compared with Vindesine as a Single Agent in the Management of Non-small Cell Lung Cancer: a Randomized Study

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Abstract—*One hundred and five patients with inoperable non-small cell lung cancer were included in a randomized trial comparing the activity of vindesine as a single agent with the combination of vindesine and cisplatin. All patients were previously untreated and the majority (70%) had squamous carcinoma. The overall partial response rates in 88 evaluable patients were 7% for vindesine alone and 33% for the combined regime. There were no complete responders in either arm. The median survival of patients treated with vindesine and cisplatin was 11 months, compared with 4 months in those treated with vindesine alone (P = 0.008). Patients showing a partial or complete response to vindesine and cisplatin survived a median duration of 13 months, compared with 7 months for non-responders (P = 0.03). This survival benefit associated with the combination was particularly apparent for patients with ECOG performance status 0 or 1 (median survival >18 months and 13 months respectively), locoregional disease (median survival 14 months) and squamous cell histology (median survival 13 months). Myelosuppression was greater with the combination but was not a major treatment problem. Neurotoxicity, which was frequently dose-limiting, was of similar severity in both treatment groups. The results indicate that the combination of vindesine and cisplatin is superior to vindesine alone for remission induction in non-small cell lung cancer and confers a significant survival advantage compared with vindesine alone in patients with favourable prognostic factors.*

INTRODUCTION

DESPITE the significant advances that have resulted from the use of combination chemotherapy for small cell lung cancer, this treatment modality has as yet made little impact upon the management of the other histological subtypes of bronchial carcinoma. Standard chemotherapeutic agents show a consistently lower order of single-agent activity in non-small cell lung cancer (NSCLC) and optimistic reports of poly-chemotherapy for these cell types have generally not been substantiated when the same drug combinations have been tested in randomized clinical trials. The focus of investigation has therefore turned upon new agents, among which vindesine and cisplatin have been shown to possess significant if only modest activity as single agents. On the basis of an overall major response rate of 19% in 194 patients [1–5], vindesine is considered by some authorities to be the most active single agent against NSCLC. Major remission rates with cisplatin have varied between 0 and 33% [6–11], with an overall response rate of 18% in 165 treated patients. Using a combination of these two agents, Gralla *et al.* [12] reported improved survival and response rates which compared favourably with those reported for conventional regimes. However,

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there have as yet been no studies that have demonstrated the superiority of this combination over the optimal use of either drug alone in an adequate number of previously untreated patients. We therefore report the results of a randomized trial in which vindesine combined with high-dose cisplatin is compared with vindesine as a single agent for the treatment of inoperable NSCLC.

MATERIALS AND METHODS

Between January 1980 and December 1982, 105 patients with histologically or cytologically verified squamous cell carcinoma, adenocarcinoma or large cell anaplastic carcinoma were entered into the study. Histological typing was in accordance with the World Health Organization classification [13]. Criteria for eligibility included the presence of assessable disease (measurable or evaluable tumour), a creatinine clearance in excess of 60 ml/min and adequate bone marrow reserve (leucocyte count $>3 \times 10^9$/l and platelet count $>100 \times 10^9$/l). Only patients who had not received prior chemotherapy or radiotherapy and who were not candidates for curative surgery were eligible. Age criteria were not specified. However, all patients were required to have an ECOG performance status of 0, 1 or 2. Clinical evidence of CNS metastasis or the presence of superior vena caval obstruction disqualified for inclusion in the trial. The characteristics of the study population are summarized in Table 2.

Pre-treatment evaluation included history, physical examination, full blood count, urinary creatinine clearance, serum electrolytes, serum aspartate aminotransferase, alkaline phosphatase and bilirubin, chest radiography, fibreoptic bronchoscopy and, in approximately half of the patients, a thoracic CT scan. Baseline audiograms were obtained in all patients prior to starting therapy with cisplatin and repeat examinations were made in most patients after three courses of treatment. On the basis of clinical staging, patients were designated as having either loco-regional disease (disease restricted to the mediastinum and ipsilateral hemithorax, but including ipsilateral and contralateral lower cervical and mediastinal nodes) or extensive disease (disease which has spread beyond the above limits).

Table 1. Evaluability for tumour response

	Vindesine	Vindesine + cisplatin
Patients entered into study	54	51
Unevaluable patients:		
No evaluable disease	4	1
Refused therapy	2	1
Severe intercurrent illness	1	–
Rapid disease progression	2	6
Evaluable patients	45	43

Patients satisfying the eligibility criteria were stratified according to cell type and disease extent and randomized to receive either vindesine (VDS) alone or VDS in combination with cisplatin (DDP). As a single agent, VDS was given i.v. in a weekly dose of 3–4 mg/m^2 depending upon toxicity for a total of 8 weeks, followed by a maintenance dose of 3 mg/m^2 i.v. fortnightly thereafter. In the combined regime VDS dosage was 3 mg/m^2 weekly for 8 weeks, without escalation, followed by the same dose fortnightly. Cisplatin 100 mg/m^2 was administered i.v. at 0, 4 and 8 weeks and every 6 weeks thereafter. Intravenous pre-hydration with 1 l of 0.9% saline over 6 hr was followed by an i.v. bolus injection of 12.5 g of mannitol. The total cisplatin dose was infused i.v. over 8 hr with 2 l of 5% dextrose in 0.5% saline, each 500 ml of infusate containing a further 10 g of mannitol. Treatment was continued beyond 8 weeks only in patients achieving at least a partial response and then up to a maximum of 8 weeks after maximal response. Chemotherapy was discontinued if there was evidence of disease progression or unacceptable toxicity. Further therapy was not specified and was left to the discretion of individual physicians. Nine (17%) and 12 (24%) of VDS- and VDS/DDP-treated patients respectively received subsequent thoracic irradiation.

Clinical assessment and blood counts were performed weekly. Treatment was delayed for 1 week if the white blood cell (WBC) count was below 3×10^9/l or the platelet count was below 100×10^9/l. If after 1 week haematological recovery resulted in values exceeding the above levels, full doses of drugs were given; if the WBC count was more than 2×10^9/l but less than 3×10^9/l or if the platelet count was more than 50×10^9/l but less than 100×10^9/l, 50% of the calculated doses of drugs were administered. If the WBC count was less than 2×10^9/l or the platelet count was less than 50×10^9/l, therapy was withheld. Estimation of urinary creatinine clearance was made prior to each cisplatin infusion. Full doses of cisplatin were given unless the creatinine clearance fell below 50 ml/min, when the drug was withheld until the creatinine clearance recovered to at least this level. VDS was withheld if severe peripheral neuropathy (moderate-to-severe weakness, foot drop, paralytic ileus) supervened, and was reduced by 50% in the presence of moderate neurotoxicity (disabling paraesthesiae, mild muscle weakness, significant sensory loss,

abdominal pain requiring analgesia or moderate constipation).

Assessment of response was carried out after 8–10 weeks' treatment or sooner in patients showing earlier evidence of tumour response or progression. Re-staging included physical examination, chest radiography, fibreoptic bronchoscopy in the majority of patients and in some cases a repeat thoracic CT scan. To be evaluable for response patients were required to have completed at least three pulses of chemotherapy (three injections of vindesine or three injections of vindesine plus one infusion of cisplatin). Response criteria were as follows: complete remission (CR) was defined as the disappearance of all known disease for at least 4 weeks; partial response (PR) was defined as a 50% or greater reduction in total tumour size without progression at any other site or the appearance of new lesions; minor regression (MR) was defined as a significant reduction in tumour size, but less than that required for the definition of PR; and progressive disease (PD) was defined as a 25% or greater increase in total tumour size.

Survival duration was recorded from the first day of treatment. Duration of response was calculated from the date the response was first noted. Assessment of survival was by the life table method and comparison of differences between the two arms was made using the log rank test. Statistical evaluation of differences in the number of responding patients was by means of the chi-square test.

RESULTS

Of the 105 patients entered into the study, five had no evaluable disease and 12 were inadequately treated having failed to complete at least three cycles of chemotherapy (Table 1). Thus, 88 patients were evaluable for tumour response. The treatment groups were well matched with respect to median age, sex ratio, performance status, extent of disease and tumour histology (Table 2). Patients in both arms received a median of eight pulses of vindesine (range 3–14 for VDS alone and 3–15 for VDS/DDP), whilst in the combination arm the median number of cisplatin treatments was three (range 1–5). The median follow-up duration was 18 months (range 4–27 months).

Details of tumour response related to histological cell type are shown in Table 3. There were no complete responses in either arm. In two patients given VDS/DDP standard chest radiographs suggested complete responses, but thoracic CT scans showed unequivocal evidence of residual tumour in both cases. Overall, in patients evaluable for response, partial remissions were obtained in 33% of cases with the combination, whilst only 7% of patients achieved a partial remission with vindesine alone ($P < 0.01$). For patients receiving vindesine and cisplatin there were no significant differences in response rate (PR + MR) with regard to performance status (43% with performance status 0/1 and 43% with performance status 2), extent of disease (39% for limited disease and 50% for extensive disease) or the evaluability of the disease (44% for measurable disease and 41% for evaluable disease) (Table 4). A significantly greater ($P < 0.02$) proportion of patients with squamous carcinoma (10/34 or 29%) achieved a partial response with vindesine and cisplatin than with vindesine alone (2/33 or 6%). The number of evaluable patients with adenocarcinoma and large cell carcinoma in both

Table 2. Characteristics of all patients entered on study

	Vindesine ($n = 54$)	Vindesine + cisplatin ($n = 51$)	Total ($n = 105$)
Median age (range), yr	61(34–74)	61(36–74)	61(34–74)
Sex:			
Male	39(72%)	37(73%)	76(72%)
Female	15(28%)	14(27%)	29(28%)
ECOG performance status:*			
0	6(12%)	7(14%)	13(13%)
1	34(67%)	33(66%)	67(66%)
2	11(21%)	10(20%)	21(21%)
Disease stage:			
Limited	37(69%)	35(69%)	72(69%)
Extensive	17(31%)	16(31%)	33(31%)
Histological cell type:			
Squamous carcinoma	37(69%)	36(70%)	73(70%)
Adenocarcinoma	7(13%)	7(14%)	14(13%)
Large cell carcinoma	10(18%)	8(16%)	18(17%)

*Performance status was not recorded in 4 patients.

Table 3. Treatment response according to tumour histology in 88 evaluable patients

Histology	Vindesine n*	PR	MR	NR	PD	Vindesine + cisplatin n*	PR	MR	NR	PD
Squamous carcinoma	33	2	1	21	9	34	10	3	20	1
Adenocarcinoma	6	1	1	3	1	2	0	0	2	0
Large cell carcinoma	6	0	0	3	3	7	4	1	2	0
Total	45	3	2	27	13	43	14	4	24	1
(%)		(6.7%)	(4.4%)	(60%)	(28.9%)		(32.6%)	(9.3%)	(55.8%)	(2.3%)

*No. of evaluable patients.
PR = partial response; MR = minor regression; NR = no response; PD = progressive disease.

Table 4. Tumour response according to prognostic factors in 43 evaluable patients given vindesine and cisplatin

	Responses PR	MR	PR + MR	Failures	Total
Tumour histology:					
Squamous carcinoma	10	3	13(38%)	21	34
Adenocarcinoma	0	0	0(-)	2	2
Large cell carcinoma	4	1	5(71%)	2	7
Performance status:*					
ECOG 0/1	12	3	15(43%)	20	35
ECOG 2	2	1	3(43%)	4	7
Disease extent:					
Limited	10	3	13(39%)	20	33
Extensive	4	1	5(50%)	5	10
Type of lesion:					
Measurable	7	0	7(44%)	9	16
Evaluable	7	4	11(41%)	16	27

*Performance status not recorded in 1 evaluable patient with progressive disease.

Table 5. Survival according to prognostic factors and tumour histology

	Median survival (months) Vindesine (n = 54)	Vindesine + cisplatin (n = 51)
All patients	4	11 $P = 0.008$
Stage:		
Limited	5	14 $P = 0.01$
Extensive	3	6 NS*
Performance status (ECOG):		
0	13	>18 $P = 0.007$
1	5	13
2	3	4 NS
Tumour histology:		
Squamous carcinoma	4	13 $P = 0.0007$
Adenocarcinoma Large cell carcinoma	4	4 NS

*NS = not significant.

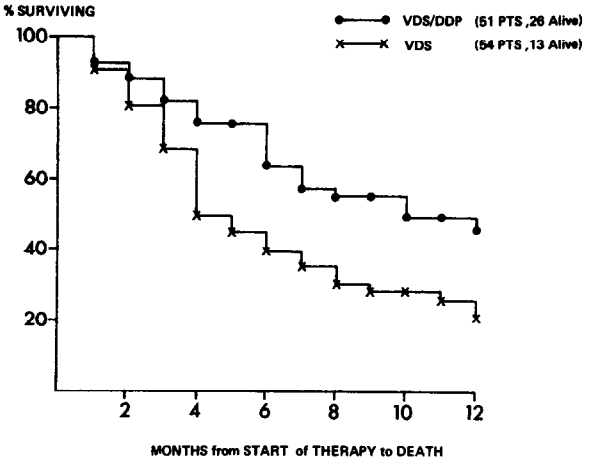

Fig. 1. Actuarial survival curves for patients treated with vindesine and cisplatin combination chemotherapy and single-agent vindesine.

treatment groups was small and statistically valid comparisons of response rates in relation to these histological cell types was not possible. The median duration of partial response was 4 months in both treatment groups. Nevertheless, significant prolongation of survival was associated with the combined treatment (Fig. 1). Median survival duration (MdST) in the vindesine arm was only 4 months, as opposed to 11 months in the combination arm ($P = 0.008$). In this latter group, survival was significantly better ($P = 0.03$) for responders (MdST = 13 months) than for non-responders (MdST = 7 months). The survival benefit associated with VDS/DDP was most apparent in patients with loco-regional disease, good performance status and tumours showing squamous cell histology (Table 5). The combination offered no significant survival advantage over VDS alone in those groups of patients with extensive stage disease, poor performance status (ECOG2) adenocarcinoma or large cell tumours, the median survival in each of these categories being about 4 months irrespective of type of treatment.

Table 6 summarizes the haematological toxicity encountered during the first 8 weeks of treatment in 78 patients for whom adequate data were available (at least four consecutive blood counts at weekly intervals). Myelosuppression was significantly greater with vindesine and cisplatin than with vindesine alone. However, the lowest leucocyte count was never less than $1 \times 10^9/l$ in either arm. Thrombocytopenia was rare and was never the cause of a bleeding problem. There was only one toxic death; this was from septicaemia in a leucopenic patient treated with vindesine/cisplatin.

Patients randomized to single-agent therapy received 91% of the scheduled protocol dose (based on 3.0 mg/m^2) of vindesine, while patients randomized to receive the combination were given only slightly less of the drug (83% of the protocol dose of vindesine). Significant neurotoxicity was encountered in 69% of patients given vindesine alone and in 53% of patients given the combination. A severe peripheral neuropathy was seen with equal frequency in both treatment groups (in four patients given vindesine alone and in three patients given vindesine/cisplatin) and was manifested by generalized weakness with or without evidence of foot drop. Weakness was usually accompanied by loss of tendon reflexes, disabling paraesthesiae or severe myalgia, but in two cases deep tendon reflexes were retained and the relatively sudden onset of severe weakness was preceded only by mild paraesthesiae and minimal sensory impairment.

Urinary creatinine clearance fell in 31 of 38 cisplatin-treated patients who were evaluable for nephrotoxicity, but the value remained below 50 ml/min in only six patients (16%), two of whom have been partial responders. In one case permanent nephrotoxicity was noted after the firt cycle of therapy. In the remainder this occurred after two ($n = 3$), three ($n = 1$) and four ($n = 1$) of cisplatin. With the exception of these six cases, nephrotoxicity was mild and of no clinical significance.

No anaphylactic reactions to cisplatin were seen. However, no patient received more than five doses of the drug. Clinically significant auditory toxicity occurred in only one patient; hearing loss was severe and was also associated with mild vestibular toxicity. One patient with pre-existing

Table 6. Haematological toxicity during the initial 8-week treatment period

	Vindesine ($n = 36$) *n*(%)	Vindesine + cisplatin ($n = 42$) *n*(%)
Lowest leucocyte count ($\times 10^9/l$):		
≤ 1.0	0(-)	0(-)
1.0–1.9	3(8)	9(21)
2.0–2.9	6(17)	17(40)
3.0–3.9	15(42)	11(26)
≥ 4.0	12(33)	5(12)
Lowest platelet count ($\times 10^9/l$):		
≤ 100	1(3)	3(7)
100–199	4(11)	18(43)
200–299	11(31)	18(43)
≥ 300	20(56)	3(7)
Median leucocyte nadir (range) ($\times 10^9/l$)	3.5(1.7–12.3)	2.8(1.0–5.1)
Median platelet nadir (range) ($\times 10^9/l$)	308(84–567)	203(50–460)

ischaemic heart disease developed acute left ventricular failure whilst receiving the fluid load accompanying cisplatin administration.

Vomiting, usually moderate or severe, occurred in 94% of patients treated with cisplatin despite the routine administration of anti-emetics, usually a phenothiazine, before and during therapy—22% of vindesine-treated patients experienced vomiting which was of either mild or moderate severity. Patients in both treatment groups commonly suffered anorexia, and weight loss of greater than 10% of body weight during the first 8 weeks of therapy was seen with equal frequency in patients given vindesine alone (19%) and those receiving the combination (16%).

DISCUSSION

The results of the present study are in support of the findings of Gralla *et al.* [12], indicating that vindesine and cisplatin is an active combination against NSCLC. The median survival of 13 months in patients responding to VDS/DDP was almost double that of non-responders (7 months) and the overall median survival in the combination arm (11 months) was significantly longer than that for patients given vindesine alone (4 months).

While some single-agent studies suggest that vindesine is equally active against all histological sybtypes of NSCLC [1, 3, 5], others have demonstrated little activity for the drug against bronchogenic squamous carcinoma [2, 4]. Thus Østerlind *et al.* found partial responses in only two of 19 tumours (11%) with this histology and in a similar phase II study reported by Mattson *et al.* no responses were observed among 21 patients with squamous cell lung cancer. Although, in the present study, only a small number of patients with non-squamous tumour histologies received vindesine alone (17, with 12 adequately treated), the response rate in this group (1/12 or 8%) was not significantly superior to that encountered among those patients with squamous cell lung cancer (2/33 or 6%). Our results therefore fail to support the existence of major differences in response rates for vindesine among the various histological cell types of bronchial carcinoma.

Cisplatin showed little activity when used as monochemotherapy for NSCLC in a number of early phase II studies [6–8]. However, these investigations were either confined to adenocarcinoma [7] or included a high proportion of patients, often with progressive disease, who had been exposed to prior chemotherapy [6, 8]. Among more recent single-agent studies, in predominantly chemotherapy naïve patients, the data are conflicting, two studies having reported major remission rates of 25% [9] and 33% [10] respectively, whilst in another study there were no responders among 24 evaluable patients [11]. In the present study the relatively low response rate to vindesine alone and the clear superiority, both in terms of response and survival, with VDS/DDP suggest that cisplatin is an important element of the combination, the results supporting the possibility of synergy between these two agents. Tumour response rates generally in the range 30–40% have been described for a variety of other cisplatin-based combinations [14–21]. Contrary, therefore, to the earlier unpromising reports of the drug's activity in NSCLC, recent studies suggest that cisplatin may well have a role in the management of this disease.

In contrast to other studies of advanced NSCLC [15, 20, 22], tumour response to VDS/DDP was as likely in poor-prognosis patients (performance status 2, extensive disease) as in patients with favourable prognostic factors. However, and in common with other reports [23], both of these variables had an important influence on survival. For VDS/DDP the overall group's median survival was prolonged compared to VDS alone, but significant benefit was restricted to those groups of patients with limited disease and good performance status.

Although both VDS and DDP may cause a peripheral neuropathy, neurotoxicity was no more severe with the combination than with vindesine alone but was, nevertheless, a major problem in both treatment groups. Our findings are in accord with those of others [5, 12] and suggest that, in further studies, a fortnightly administration schedule should be preceded by a maximum of five weekly doses of vindesine. There were no drug-related deaths due to renal failure. However, a permanent fall in creatinine clearance, prohibiting further therapy with cisplatin, occurred in six patients. Thus renal impairment, though ameliorated [24], was not completely preventable with mannitol-induced diuresis and this nephrotoxicity may be enhanced by the addition of other cytotoxic agents, e.g. bleomycin [19]. Myelosuppression was greater with the combined regime than with vindesine alone and was responsible for one death, but leucopenia was, nevertheless, relatively infrequent in both groups. As with other series, vindesine appeared to exert a platelet-sparing effect and thrombocytopenia was a rare occurrence.

In conclusion, this study has demonstrated the superiority of VDS/DDP over VDS alone in the treatment of advanced NSCLC. It adds to the growing number of reports indicating the potentially useful activity of cisplatin containing combinations in this disease and supports the

further evaluation of such regimes as adjuvant therapy in resectable NSCLC and in combination with radiotherapy for inoperable disease.

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