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Phase II trial of vindesine and VP16-213 in the palliation of poor-prognosis patients and elderly patients with small cell lung cancer

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Summary. *Forty-three previously untreated patients, all of whom had poor-prognosis small cell lung cancer and/or were > 65 years old, received treatment with vindesine and VP16–213. Thirteen patients had limited disease and 30 extensive disease. Response rates (CR + PR) of 86% (CR 29%) and 66% (CR 17%) were seen in patients with limited and extensive disease, respectively. Time to relapse was short in those responding (4–4.5 months), and most responders required additional treatments. The overall toxicity was minimal and patient compliance was high. This combination is useful for the palliative treatment of small cell lung cancer when aggressive chemotherapy is inappropriate.*

Introduction

Small cell carcinoma of the bronchus (SCCB) is very responsive to combination chemotherapy, with response rates of up to 80% regularly reported [2]. Though complete responses (CR) of over 50% can be expected in patients with limited disease, this falls to around 20% in those with extensive disease, and overall median survival in these two groups is 14+ months and 7+ months, respectively [9]. To achieve such results aggressive and moderately toxic combination chemotherapy is necessary.

The synthetic vinca alkaloid vindesine has shown considerable single-agent activity in SCCB, with response rates (CR + PR) of around 25% [8, 10, 14]. The epipodophyllotoxin VP16–213 (Bristol-Myers) has proved to have response rates in SCCB of between 10% and 65% (mean 40%) [5] when used as a single agent. Both vindesine and VP16–213 have proved to cause relatively low toxicity at effective dose levels. The present study reports the activity of the combination of vindesine and VP16–213 given as palliative therapy to patients with a poor prognosis by virtue of performance status and extent of disease and to patients considered too old and infirm to tolerate intensive and toxic chemotherapy.

Patients and methods

Forty-eight patients (27 male, 21 female: age 44–75, mean 65.1 years) who had histologically or cytologically proven small cell lung carcinoma, and were over 65 years, had a poor performance status, or had extensive disease were included in the study. Five patients were not evaluable for response. Of these, three died of unrelated causes (peritonitis secondary to colonic diverticulum, pseudomembranous enterocolitis, and probable myocardial infarction) and two deaths were related to (presumed) toxicity. Thirty-five patients had evidence of extensive disease, 30 were over 65 years, and 17 were over 65 and had extensive disease. All patients were previously untreated, with the exception of two who had had prior mediastinal irradiation for superior vena caval obstruction (SVCO) and three who had had prior brain irradiation, though all these five patients had evaluable disease outside the radiotherapy fields. Patient characteristics with reference to performance status and age are shown in Table 1. The sites of extrapulmonary disease in the forty-three evaluable patients are listed in Table 2.

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Table 1. Patient characteristics (age, extent of disease, and performance status) on admission to the study

Category	Performance status (ECOG)				
	0	1	2	3	Total
Age > 65[a]	2	11	15	2	30
Age < 65	0	6	5	2	13
Total	2	17	20	4	43
Limited disease	0	6[c]	7	1	14
Extensive disease	2[b]	11	13	3	29
Total	2	17	20	4	43

[a] Mean 65.1 (range 44–75) years
[b] Both these patients were 71 years old
[c] Only one patient under 65 years old in this group

Table 2. Sites of extension in 29 patients with extensive disease

	No.
Single site of extension	18
Nodal or SC	7 (5 > 65 years)
Liver	5
Bone/bone marrow	3
Brian	1
Effussion	2
Multiple sites of extension	11 (6 > 65 years)

The Veterans Administration Lung Cancer Study Group definition of limited and extensive disease was used [11]. Staging procedures were kept to a minimum, only complete blood count, urea, electrolytes, liver function tests, (AST, LDH, alkaline phosphatase, and bilirubin), and chest radiography with a barium swallow being done routinely. If there was clinical suspicion or biochemical/radiological evidence for extension the patient concerned underwent one or more of the following tests: liver ultrasonography, radio-isotopic bone scanning, bone marrow aspiration/trephine, and CT scan of the cranium.

Drug administration. Vindesine (3 mg/m^2 up to max. 5 mg) was administered by IV bolus into the side arm of a fast-running drip with the subsequent administration of VP16–213 (120 mg/m^2 in 500 ml 0.9% saline) over 1 h, the VP16–213 infusion being repeated on days 2 and 3. The cycle was repeated 3-weekly, with assessment of response after three courses. Responders completing six treatment cycles had appropriate restaging. No patient required dose modification and all responders have completed all six treatment cycles to date.

Complete response (CR) is defined as the complete disappearance of all symptoms and signs of disease lasting a minimum of 30 days. partial response (PR) is defined as a 50% or more reduction in assessable lesions, using the cross perpendicular dimensions of each lesion, lasting a minimum of 30 days.

Toxicity. Toxicity was assessed using the WHO criteria [13].

Results

Forthy-three patients were evaluable for response to V/VP16 (Table 3). The overall response rate was 72% (21% CR). Predictably, it was higher in patients with limited disease (86%; 29% CR) than in patients with extensive disease (66%; 17% CR). No response was seen in 12 of 43 patients (28%). The mean duration of response is 4.5 months for complete responders and 4 months for partial responders. Median survival for responders in 10 months, with limited-disease patients surviving a median of 12 months and extensive-disease patients 8 months. The median survival of nonresponders is 5 months. The overall response rate was 72%, giving a median overall survival of 8 months and a 12-months survival figure of 23%. Limited-disease patients showing a response had a 12-months survival of 60% and the corresponding figure for extensive-disease patients is 20%.

Nine of 43 patients achieved CR, which in five of these nine was confirmed by bronchoscopy. Median survival of complete responders is 13 months. Twenty-one of the 31 who relapsed did so at the primary site. Details of the further treatment of relapsing patients are listed in Table 4. Of the twelve nonresponders, six received methotrexate, cyclophosphamide, and CCNU with one CR, one PR, and four failures to respond. Responders, however, like nonresponders, generally tended to lose weight throughout treatment.

Table 3. Summary of results

	Response rate	No.	Median survival	12-month survival
Limited disease	CR 29%	4	13 month	75%
	CR + PR 86%	8	12 month	60%
Extensive disease	CR 17%	5	12 months	60%
	CR + PR 66%	14	8 months	20%
Nonresponders		12	5 months	10%
Overall	72%	43	8 months	23%

Table 4. Details of second-line treatment in 31 relapsing patients

	No.	Response
Vindesine and VP16 retreatment	5	2 CR, 2 PR
MCC[a]	6	1 CR, 5 PR
Mediastinal irradiation	11	
Brain irradiation	2	
No further therapy	14	

[a] Methotrexate, cyclophosphamide, and CCNU

Toxicity

The predominant toxicity, as shown in Table 5, is alopecia, with nausea/vomiting a very minor problem and neurotoxicity mild and reversible. Haematological toxicity was not a problem, only two patients having therapy delayed for 1 week due to neutropenia. The two presumed toxic deaths in patients with marrow involvement indicate that severe marrow suppression can occur with this combination.

Discussion

The single-agent activity of both vindesine and VP16–213 suggested that these agents in combination would be highly active in SCCB. As minimal toxicity was anticipated with this regimen, only patients who were older than 65 or had poor performance status or extensive disease – in general patients considered unsuitable for aggressive chemotherapy – were admitted to the study, the aim of treatment being palliation. Aggressive chemotherapeutic regimens offer substantial benefit to patients with limited disease, but the benefits are less clear for patients with extensive disease at presentation [1, 3, 4, 6, 12]. In patients with poorer prognosis and those are less able to tolerate or indeed survive aggressive chemotherapy, a shorter median survival, with palliation of symptoms and minimal toxicity, may be an acceptable goal. Nonaggressive treatment of elderly patients was a further goal of this study. Indeed, a recent report of oral cyclophosphamide, oral procarbazine, oral methotrexate and IV vincristine in attenuated doses has demonstrated a 1-year survival of 59% and an 18-months survival of 30% with consolidation radiotherapy in limited-disease patients, and toxicity, was extremely low [7]. In this study the overall response rates in both limited (86%) and extensive (66%) disease compare favourably with the rates in other studies [2], though the CR rate was low at 28% in limited disease and 17% in extensive disease compared with studies employing three- or four-drug combinations, where CR rates of 44%–77% for limited disease and 21%–52% for extensive disease [9] have been reported. Duration of response is disappointingly short at 4–4.5 months, though the median survival of complete responders is 13 months, with a 12-month survival of 68% in this group. Two of four CR patients retreated with V/VP16 again obtained CR, and in view of the

short duration or remission prolongation of therapy with V/VP16 may be warranted.

Six patients who relapsed were treated with methotrexate, cyclophosphamide, and CCNU (MCC) with all six responding, confirming the likelihood of non-cross resistance with this combination. Toxicity was increased for these patients, however, and two of the six failed to complete the full course of MCC.

The lack of toxicity from V/VP16 was impressive (Table 5), with reversible alopecia the main side-effect and almost universal. Myelotoxicity caused concern only in the two patients with marrow involvement, who died of suspected toxic deaths due to neutropenia. Nausea was uncommon and only three patients had mild vomiting lasting a few hours. Neurotoxicity was an inconvenience for six patients (20%; WHO grade 1–2), who have nonetheless completed six courses of V/VP16, since it never necessitated discontinuation of treatment and was reversible within a few weeks.

Most responding patients demonstrated an increase in performance status, as shown in Table 6. Good palliation of symptoms was achieved in responding patients with minimal toxicity. Though median survival overall is lower than in many reported series for SCCB, a more aggressive regimen, whilst extending the median survival of patients, would lead to much greater toxicity and probably a larger number of treatment-related deaths. The advantages of V/VP16 are the minimal toxicity experienced and the increased performance status for the majority of responders at the end of treatment. Although the time to relapse is disappointingly short this may be prolonged by continuing treatment beyond six courses or using mediastinal irradiation as consolidation in responders with limited disease at presentation.

Table 5. Overall toxicity in 30 patients completing six courses of V/VP16 treatment

	No.	WHO grade
Haematological	2	1
	2	2
Neurotoxicity	6	1–2
Alopecia	30	2–3
Constipation	1	3
Nausea/vomiting	5[a]	1
	3[b]	2

[a] Mean duration 1.5 days
[b] Mean duration 1 day

Table 6. Changes in performance status (responders)

Performance status	No. prior to therapy	No. after therapy
0	2	16
1	10	12
2	16	3
3	3	0

It has to be recognised that for the majority of patients with SCCB, intensive and toxic chemotherapy is unlikely to produce a durable clinical remission of disease. In the absence of clearly superior chemotherapy it seems reasonable to adapt our aim to palliation for patients who have poor prognostic features or who are unlikely to tolerate severe toxicity. Whithin this context, it appears that this regimen is an acceptable treatment.

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