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Phase II Study of Vinorelbine (Navelbine) in Previously Treated Small Cell Lung Cancer Patients

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26 previously treated patients with progressive recurrent small cell lung cancer (SCLC) were given vinorelbine (Navelbine), 30 mg/m² weekly. All patients had responded to first-line chemotherapy and were off therapy for at least 3 months. Partial response was observed in 4 out of 25 eligible patients (16%; 95% confidence interval 4–36%), stable disease in 7 patients and progression in 12 patients. The limiting toxicity was a non-cumulative leucopenia (80%, 32% WHO grade 3–4). Reaction at the site of injection was observed in 5 patients, causing treatment discontinuation in 2 cases. Other non-haematological toxicities were moderate. These results suggest acceptable toxicity and some antitumour activity of vinorelbine in pretreated SCLC patients.
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INTRODUCTION

VINORELBINE (5'-NOR-ANHYDROVINBLASTINE, Navelbine) is a new semisynthetic vinca alkaloid, which was selected for its high affinity to prevent tubulin polymerisation [1]. *In vivo* studies performed on human tumours xenografted in nude mice showed the activity of vinorelbine against different types of lung carcinoma [2]. In most lung cancer xenografts vinorelbine compared favourably with vincristine and vinblastine [2]. Clinical phase I studies showed dose-related leucopenia, while other toxicities were moderate [3, 4]. The recommended dose for phase II studies was 30 mg/m², intravenously (i.v.) weekly. Further clinical studies demonstrated cytotoxic activity of vinorelbine in several tumours, including non-small cell lung cancer [5–7]. Because of these interesting results the EORTC Lung Cancer

Cooperative Group initiated a phase II study in small cell lung cancer to assess antitumoral activity of vinorelbine and to delineate further its toxicity using a recommended treatment schedule.

MATERIALS AND METHODS

Patients could enter the study provided the following criteria were fulfilled: histologically or cytologically confirmed progressive recurrent small cell lung carcinoma not amenable for curative surgery or radiation therapy, response to first-line chemotherapy (one regimen allowed) and previous chemotherapy discontinued at least 3 months before entering this protocol. Patients were required to have measurable or evaluable disease outside of previously irradiated area. No brain involvement or leptomeningeal disease was allowed unless it was controlled by radiotherapy. Other criteria for exclusion were previous or current malignancies at other sites (with the exception of cone biopsied *in situ* carcinoma of the cervix and adequately treated basal or squamous cell carcinoma of the skin), poor medical risks beause of non-malignant systemic disease, active, uncontrolled infection and peripheral neuropathy. Prior to entry patients were required to have adequate bone marrow reserve [white blood cell (WBC) $> 4 \times 10^9$/l, platelets $> 100 \times 10^9$/l] and kidney function (serum creatinine < 150 μmol/l).

Vinorelbine was administered at the dose of 30 mg/m^2 weekly, by i.v. infusion in 250 ml of normal saline over 20 min, followed by an infusion of 100 ml normal saline. Treatment was discontinued if there was disease progression or severe toxicity or if the disease remained unchanged after six courses. Dosage adjustments were made according to the value of WBC and platelets measured before each cycle. Drug administration was postponed by 1 or 2 weeks if there was no full haematological recovery (WBC $> 4 \times 10^9$/l, platelets $> 100 \times 10^9$/l) from the prior course. The dosage of the due course was then adjusted according to the nadir value of WBC and platelets after the prior course: for WBC values of 2.0–2.499 $\times 10^9$/l and platelet values of 75–99.999 $\times 10^9$/l the dose was reduced to 75% and for values $< 1.999 \times 10^9$/l and $< 74.999 \times 10^9$/l, respectively, to 50%. If the treatment was delayed by 3 weeks or more, the patient went off study.

The initial evaluation included physical examination, measurement of indicator lesions, electrocardiogram, blood cell counts, differential and chemistry.

Response was evaluated every three cycles. Definition of response and toxicity followed WHO criteria [8]. The trial was done according to "good clinical practice" guidelines [9].

RESULTS

From June 1990 to May 1991, 26 patients from eight institutions were registered (Table 1). 1 patient was ineligible because of receiving previously two chemotherapy regimens. All other patients received one prior chemotherapy regimen (median three drugs, range two to seven) and responded to first-line chemotherapy (11 patients with complete remission and 14 patients with partial remission). 15 patients received prior radiotherapy. Median age was 59 years (range 41–73 years) and sex ratio was 3.2 : 1 (19M : 6F). Median WHO performance status was 1 (0–2).

Table 1. Patients' characteristics

Sex	
Males	19
Females	6
Median age in years (range)	59 (41–73)
Median WHO performance status (range)	1 (0–2)
Prior chemotherapy	25
Median no. of drugs (range)	3 (2–7)
Response to previous chemotherapy	
CR	11
PR	14
Prior radiotherapy	15

A median of three cycles (range two to 13) was administered. 23 patients were evaluable for response. 2 patients were unevaluable: 1 patient due to treatment withdrawal for toxicity after 2 cycles and 1 patient due to cardiovascular death after 3 cycles. The latter had been previously treated with doxorubicin with a total dose of 230 mg, but his death was deemed not to be related to subsequent therapy with vinorelbine. These two events were considered as treatment failures and both patients were included in the analysis (Table 2). 4 patients achieved partial remission (16.0%; 95% confidence interval 4–36%), 7 patients had stable disease and 12 patients had primary progression. Site of response included primary sites (four partial responses), lymph nodes (two complete responses and one partial response), liver (one partial response) and bone (one partial response). In 3 patients the response was first noticed after three cycles and in 1 patient after six cycles. All responses were externally reviewed. Duration of response was 17 weeks for 2 patients, 16 weeks for 1 patient and 9.5 weeks for 1 patient.

Toxicity was moderate and in most cases manageable (Table 3). In 3 patients treatment was stopped due to side-effects (2 patients grade 3 phlebitis and 1 patient grade 3 neurotoxicity). The most common toxicity was leucopenia, which occurred in 80% of patients (grades 3–4 in 32%). Twenty-eight per cent of patients had a leucopenia-caused treatment delay, 8% had a dose reduction of 50% and 24% of patients had a dose reduction of 25%. No thrombocytopenia was observed and grade 1–3 anaemia occurred in 44% of patients. Neurotoxicity included 4 cases of mild paresthesia, 1 case of moderate paresthesia and 1 case of severe paresthesia and weakness. The latter two had been previously treated with cisplatin. Local reaction was observed in

Table 2. Response to treatment

	No.	%
Partial response	4	16 (confidence interval 95%: 4–36)
No change	7	28
Progression	12	48
Stop for toxicity	1	4
Early death	1	4
Total	25	100

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Table 3. Toxicity (n = 25)

	WHO grade				
	1	2	3	4	Total (%)
Leucopenia	5	7	7	1	20 (80)
Neutropenia	—	10	4	4	18 (72)
Thrombocytopenia	—	—	—	—	—
Anaemia	10	—	1	—	11 (44)
Nausea/vomiting	6	4	—	—	10 (40)
Diarrhoea	3	1	—	—	4 (16)
Drug fever	4	2	—	—	6 (24)
Local skin reaction	2	2	1	—	5 (20)
Local phlebitis	—	—	2	—	2 (8)
Alopecia	3	—	—	—	3 (12)
Infection	—	1	—	—	1 (4)
Mucositis	1	—	—	—	1 (4)
Cardiotoxicity	1	—	—	—	1 (4)
Neurotoxicity	4	1	1	—	6 (24)
Bone pain	1	2	—	—	3 (12)
Other	3	—	—	—	3 (12)

5 patients. Other non-haematological toxicities were usually moderate.

DISCUSSION

Testing new drugs in SCLC is a difficult problem due to ethical aspects of depriving patients with a grim prognosis of a potentially effective treatment. Several approaches are possible as was described by Ettinger [10]. During the third IASLC workshop on SCLC the concept of patients with a clinically resistant or sensitive tumour was launched [11]. This concept is based on *in vivo* observations in patients with tumour progression [12, 13]. Clinically resistant tumours are those who have relapsed during treatment or within 3 months after the last chemotherapy cycle, and possible sensitive tumours are those relapsing later. The EORTC Lung Cancer Cooperative Group has accepted hypothetically optimal conditions for detecting activity of new drugs with minimal risk of giving possible inactive therapy to patients with a chance for long-term disease-free survival. These conditions include evaluation of new drugs in pretreated patients who had response to initial chemotherapy and who relapsed 3 or more months after cessation of treatment. The present study employed this approach. The results presented here suggest modest activity of vinorelbine given alone in pretreated patients with SCLC. Since the application of the described concept is still new and this is probably the first study based on this approach, it is unclear what response rates indicate useful sensitivity and whether the standard number of 25 patients is adequate to give meaningful conclusions.

The response rate observed here is similar to those reported for other single agents including etoposide and teniposide if given in second-line setting [14, 15]. In contrast to the low activity of these two agents in pretreated patients, they have demonstrated high activity in first-line treatment [16, 17].

The toxicity of vinorelbine was moderate compared to other currently used drugs. The only limiting toxicity was leucopenia. Other side-effects were usually mild, including neurotoxicity, which is the major toxicity of other vinca alkaloids. This, together with the observed response rate warrants further evaluation of this drug in previously untreated patients in order to define the real response rate and to test the usefulness of the approach described above. Such testing should include strict early stopping rules and a crossover to an active rescue treatment for non-responding patients.

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