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Phase I–II Study of Vinorelbine (Navelbine®) plus Cisplatin in Advanced Non-small Cell Lung Cancer

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32 patients with advanced non-small cell lung cancer previously untreated by chemotherapy were included in a phase I–II study in order to determine the feasibility of the combination of vinorelbine and cisplatin, each administered at its optimal dose, i.e. 30 mg/m² weekly and 120 mg/m² every 4–6 weeks, respectively. There were 27 males and 5 females with a mean age of 55 years and a median performance status of 80%. 13 had locally advanced disease and 19 had distant metastases at the time of inclusion. Our study demonstrated the feasibility of this protocol. Dose intensities could be maximised by adapting vinorelbine doses rather than by postponing treatment in the event of neutropenia. Both response rate (33%) and overall survival of the population (median 11 months) justify further studies.
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INTRODUCTION

THE HIGH proportion of patients with non-small cell lung cancer (NSCLC) inoperable at the time of presentation because of locally advanced or disseminated disease explains the numerous attempts at developing new systemic combination therapies over the last years. This disease remains the major cause of death from cancer in males in Western countries [1].

To date, few drugs have demonstrated their efficacy as a single agent in the multiple phase II studies conducted in NSCLC [2]. Recently, a new hemi-synthetic vinca alkaloid, vinorelbine (Navelbine), has been added to the group of so-called 'active' cytotoxic agents which yield a 15% or more objective response rate. A 33% response rate has been reported in 69 previously untreated patients (26% in patients with stage IV disease and 29% in patients with stage III and IV). Its tolerance was good, with low peripheral neurotoxicity. The limiting toxicity was neutropenia [3].

The two-drug combination of cisplatin and vindesine has been widely studied in the last decade. A trend towards a survival benefit has been observed in most studies, reaching a significant difference in a Canadian multicentre randomised trial when compared to the 'best supportive care' arm [4].

It was therefore considered worthwhile to evaluate the combination of vinorelbine and cisplatin in NSCLC. The first step was to determine the feasibility of this combination.

Cisplatin was administered at a dose of 120 mg/m². The rationale for this dose was based on the randomised study which demonstrated the superiority of high-dose compared to lower dose of cisplatin [5]. Vinorelbine doses were escalated with the intention of reaching 30 mg/m² weekly, the level at which its efficiency was demonstrated in the phase II single agent study [3]. In order to avoid any unexpected toxicity of the combination, it was decided to apply an empirical 33% dose reduction of vinorelbine in the first patients and to initiate vinorelbine at the 20 mg/m² weekly dose.

PATIENTS AND METHODS

From April 1988 to February 1989, 32 patients with advanced NSCLC entered in this phase I–II study of vinorelbine–cisplatin administered as first line chemotherapy. All patients fulfilled the following eligibility criteria: histologically proven NSCLC, inoperable at the time of presentation, no previous chemotherapy, life expectancy > 3 months, performance status (Karnofsky index) ≥ 70%, at least one measurable lesion, granulocyte count ≥ 2.000/μl, platelet count ≥ 100.000/μl, normal creatinine and bilirubine levels, absence of neuropathy and informed consent. In the case of previous radiotherapy, patients had to have a full recovery from any toxicity before inclusion. Patient characteristics are summarised in Table 1.

Cisplatin was administered at a dose of 120 mg/m² intravenously with a 24-h hydration on day 1, 29 and every 6 weeks thereafter. Vinorelbine was diluted in 125 ml of normal saline and administered intravenously over 15 min. The vein was then washed out with a further 125 ml of normal saline for 30 min. Three successive incremental dosage levels of vinorelbine were tested: 9 patients received a weekly dose of 20 mg/m², 6 patients 25 mg/m² and 17 patients 30 mg/m². The treatment had to be postponed for the first 24 patients until the granulocyte count recovered to ≥ 2.000/μl. In order to maintain the rhythm of administration of cisplatin every 4 then 6 weeks as in the reference studies [4, 5] and to administer a maximum weekly dose of vinorelbine, the last 8 patients received 100% of the weekly dose of vinorelbine if granulocyte count was > 1500/μl, 50% of the weekly dose if granulocyte count ranged 1000–1500/μl and no treatment in case of neutropenia < 1000/μl. Thus, cisplatin could be given at the planned date. Chemotherapy was pursued until either disease progression or unacceptable toxicity or patient refusal. Another treatment modality was

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Table 1. Patients' characteristics

Patients	32
Evaluable for response	30
Male: female	27:5
Age (years)	55 (37–66)
Histology	
Adenocarcinoma	18
Large cell	9
Squamous cell	5
AJC classification	
Stage IIIA	2
IIIB	11
Stage IV	12
Metastatic*	7
Median performance status	80% (70–100)

*Metastatic after previous surgery and/or thoracic radiotherapy.

then proposed according to the disease status. Response was established on clinical examination, chest X-ray, ultrasound and/or computed tomography (CT) scan according to the evaluated lesions. Response and toxicity were scored according to WHO criteria [6].

RESULTS

Clinical tolerance was good, as shown in Table 2, with mild alopecia (only one grade 3, no grade 4) and nausea or vomiting never exceeded grade 2 in patients who received conventional antiemetic therapy during each cycle of cisplatin. Local tolerance was acceptable and all treatments were administered without a central venous access. Two patients experienced a peripheral neuropathy which led to discontinuation of treatment after 6 months, despite the fact that a partial response had been achieved in both cases. Another patient experienced transient grade 1 renal failure, hence the reason for a reduction in the cisplatin dosage by a third. This transitory episode of renal failure did not result in a subsequent impairment of renal function.

The dose intensity compliance of vinorelbine and cisplatin, evaluated at the 11th week just after the third planned administration of cisplatin, was increased for the 8 patients treated at the 30 mg/m² dose level with dose adaptation of vinorelbine, as shown in Table 3.

Haematological toxicity was almost exclusively observed on granulocytes (Table 4). It increased with the higher dose intensity but no patient experienced a septic complication requiring hospitalisation. No patient experienced thrombocytopenia. It should be noted, however, that 5 patients developed thrombocytosis exceeding 500,000/μl (5% of cycles).

Of the 32 patients included in the study, 2 were not evaluable for response, because their only measurable lesion had been previously irradiated. Another 2 patients were considered minor protocol deviations because they received inadequate doses of cisplatin (105 mg/m² each, total dose 210 mg for 1 patient and 240 for the other). The latter 2 patients were only included in the evaluation for response and were not evaluated for biological tolerance.

None of the 9 patients who were treated at the 20 mg/m² dose level of vinorelbine achieved an objective response. The response rate at this step was less than 20% with a 95% confidence interval dose. At the 25 and 30 mg/m² levels, seven partial responses (PR) were obtained among the 21 evaluable patients (33%) (95% C.I.: 13–53%; Table 5). 5 of these 7 responders had stage IV

Table 2. Non-haematological toxicity (n = 32 patients)

	WHO grading* (%)			
	0	1	2	3
Nausea—vomiting	19	34	47	0
Alopecia	75	16	6	3
Local reaction	66	34	0	0
Paresthesia	78	13	9	0
Constipation	97	3	0	0
Stomatitis	97	3	0	0
Diarrhoea	97	3	0	0
Renal failure	97	3	0	0

*No patients had grade 4 toxicity.

Table 3. Dose intensity of vinorelbine and cisplatin for the first 10 weeks of treatment

Theoretical weekly dose of vinorelbine (mg/m²)	Received dose/theoretical dose (%)	
	Vinorelbine	Cisplatin
20	73	67
25	73	67
30	68	72
30+ adaptation	77	95

Table 4. Haematological toxicity (neutropenia)

Weekly dose level of vinorelbine		n	Grade WHO (%) 0	1	2	3	4
20 mg/m²	Patients	9	33	22	11	34	0
	Cycles	62	74	8	11	7	0
25 mg/m²	Patients	4	0	0	75	25	0
	Cycles	60	65	10	23	2	0
30 mg/m²	Patients	9	11	11	11	45	22
	Cycles	55	62	11	15	9	3
30 mg/m² with dose adaptation	Patients	8	0	0	25	25	50
	Cycles	75	45	15	12	16	12

n = Number of evaluable patients or cycles.

Table 5. Responses according to the dose of vinorelbine

	Dose level of vinorelbine (mg/m²)			
	20	25	30	Total
Evaluable patients	9	5	16	30
Stage IIIA	0	1	1	2
Stage IIIB	3	3	5	11
Stage IV or M+	6	1	10	17
PR	0	2	5	7
NC	4	3	6	13
PD	5	0	5	10

PR = partial response; NC = no change; PD = progressive disease.

disease and the remaining 2 patients had stage IIIA and stage IIIB disease. 3 had an adenocarcinoma, 3 had a large cell carcinoma and 1 patient had a squamous cell carcinoma. Treatment was discontinued in 2 of those 7 patients because of progression after 13 and 36 weeks. As the other 5 responding patients received subsequent therapy (surgery plus radiotherapy in 1 case and radiotherapy in 4 cases) after vinorelbine–cisplatin in order to sustain response, the median duration of response to chemotherapy alone is 30+ weeks. For the entire population, time to progression ranges from 4 to 100 weeks (median 20).

The median duration of survival is 11 months. 7 patients are still alive after 8+, 19+, 19+, 22+, 24+, 26+ and 31+ months of follow-up. Among them, 2 had a partial response to chemotherapy (1 stage IIIB, 1 stage IV) and 5 were considered as no change. Among those last 5 patients, 3 had metastatic disease at the time of inclusion in the present study, which had occurred after initial local treatment.

CONCLUSION

The present phase I–II study allowed us to demonstrate the feasibility of high-dose cisplatin combined with vinorelbine when the latter is administered at 30 mg/m^2 according to the weekly schedule which established its efficacy as a single agent. Cisplatin and vinorelbine dose intensities could be maximised by adjusting vinorelbine dosage according to neutropenia since neither grade 3 nor grade 4 neutropenia involved life-threatening sepsis in the present study. Interestingly, the threshold dose of vinorelbine, below which no objective response was observed in this study, is 25 mg/m^2. This fact should be kept in mind for the design of future protocols including vinorelbine.

Considering the results previously reported with vinorelbine alone, both the response rate and response duration observed in the present study deserve further randomised trials in order to determine the exact role of vinorelbine alone or combined with cisplatin in the treatment of advanced NSCLC.

1. Silverberg E, Lubera J. *Cancer Statistics* 1986, **36**, 9–25.
2. Klastersky J, Sculier JP. Non-surgical combined modality therapies in non-small cell lung cancer. *Chest* 1986, **89**, 289–294.
3. Depierre A, Lemarié E, Dabouis G, *et al.* A phase II Study of Navelbine (vinorelbine) in the treatment of non-small cell lung cancer. *Am J Clin Oncol* 1991, **14**, 115–119.
4. Rapp E, Pater J, William A, *et al.* Chemotherapy can prolong survival in patients with advanced non small cell lung cancer. Report of a Canadian multicenter randomized trial. *J Clin Oncol* 1988, **6**, 633–641.
5. 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 Int Med* 1981, **95**, 414–420.
6. WHO. Handbook for reporting results of cancer treatment. *Genève WHO Offset Publ* 1979, **48**.

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Surgical Treatment of Myeloma of Bone

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33 patients treated operatively for plasma cell disease were analysed. There were 21 men and 12 women with an average age of 54 years. There was an undefined bone tumour in 23 cases, and a pathologic fracture in 10 cases. In only 6 cases was the diagnosis known before the operation. The primary tumour localisations were: vertebral column in 13, pelvis in 7, femur in 6, humerus in 2, rib in 1, tibia in 1, fibula in 1, scapula in 1 and olecranon in 1 case. 16 diagnostic biopsies were taken. Vertebral tumours were mainly evacuated or decompressed, combined with a stabilising procedure in 8 cases. A total of six endoprotheses, five to the femur and one to the humerus were performed. Two primarily wide resections, to the fibula and to the scapula were done. There were no locally recurring tumours during a mean follow-up time of 4 years and 2 months, and we conclude that operative and oncologic treatment is successful in providing the patient with a stable, pain-free locomotive system.
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INTRODUCTION

THE TREATMENT of myeloma consists of chemotherapy and irradiation, and nowadays bone marrow transplantation is also used in selected cases [1]. Surgical intervention is necessary in cases of solitary plasmacytoma of bone and in complications of multifocal myeloma. Solitary plasmacytoma of bone is a localised plasma cell tumour that accounts for about 5% of malignant plasma cell diseases [2]. The most common location is the vertebral column [3]. The usual treatment of plasmacytoma of bone is a combination of surgery and radiotherapy [4]. The expected survival rate is 45–85% 10 years after the diagnosis [5, 6]. In multifocal myeloma, surgery is usually needed because of a pathologic fracture and is aimed to reduce pain and allow early mobilisation.

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PATIENTS AND RESULTS

The patients treated operatively for solitary plasmacytoma or multiple myeloma in the Department of Orthopaedics and