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Short Communication

Vinorelbine/Gemcitabine in Advanced Non-small Cell Lung Cancer (NSCLC): a Phase I Trial

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Vinorelbine and gemcitabine are both active as single agents in advanced non-small cell lung cancer (NSCLC). Because of their different mechanisms of action, good tolerability and possible administration on an out-patient basis, vinorelbine/gemcitabine should be an interesting combination for palliative chemotherapy. Thus, we initiated a phase I dose-escalation trial in order to determine the maximum tolerated doses of vinorelbine/gemcitabine that can be administered without haematopoietic growth factors, the dose-limiting toxicities and the most frequent side-effects of this novel combination. 40 chemotherapy-naïve patients with advanced NSCLC were treated with different doses of vinorelbine/gemcitabine on days 1, 8 and 15, and this treatment cycle was repeated on day 29. Vinorelbine and gemcitabine were escalated from 10 to 30 mg/m^2 and 600 to 1200 mg/m^2, respectively. A total of 63 treatment cycles were administered and 27 patients received at least two treatment cycles. Dose-limiting toxicities were leucopenia plus thrombocytopenia (2 patients) and mucositis (1 patient). The maximum tolerated dose was established at 25 mg/m^2 vinorelbine combined with 1200 mg/m^2 gemcitabine. Frequent side-effects were leucopenia, anaemia, nausea/vomiting, flu-like symptoms, skin rashes and elevation of liver enzymes. The recommended phase II doses are 20–25 mg/m^2 vinorelbine combined with 1000–1200 mg/m^2 gemcitabine on days 1, 8 and 15, but myelosuppression will have to be carefully monitored. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

PALLIATIVE CHEMOTHERAPY is increasingly recognised as an important treatment modality of advanced non-small cell lung cancer (NSCLC) [1] and its impact is further enhanced by new anticancer drugs [2, 3]. In particular, drugs with good tolerability and easy administration, such as vinorelbine and gemcitabine, lend themselves to palliative treatment. Vinorelbine [4–6] and gemcitabine [7–10] have shown activity as single agents in advanced NSCLC. The maximum tolerated doses as single agents have been established for vinorelbine at 30–35 mg/m^2 [11], and for gemcitabine at 790 mg/m^2 in pretreated patients [12] and 2200 mg/m^2 in chemotherapy-naïve patients [13]. Because of their different mechanisms of action, good tolerability and similar schedules of administration on an out-patient basis, vinorelbine/gemcitabine might be an interesting combination for palliative treatment of advanced NSCLC and other solid tumours. To further pursue this, we initiated a phase I trial in order to determine the maximum tolerated doses, the dose-limiting toxicities and the toxicity profile of this novel combination without prophylactic administration of haematopoietic growth factors.

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PATIENTS AND METHODS

Chemotherapy-naïve patients with advanced NSCLC were entered into this phase I trial which had been approved by the local ethical committees. Further inclusion criteria were age < 75 years, good performance status (Karnofsky > 60%), adequate organ function and written informed consent. Exclusion criteria were cerebral metastases (except in clinical remission after radiotherapy), active infection and pregnancy.

Pretreatment evaluation included medical history, physical examination, complete blood cell count, liver and renal function tests, electrocardiogram (ECG), and a complete tumour staging that included a chest X-ray, a computed tomography (CT) scan of the lungs and mediastinum, and a CT scan or ultrasonography of the liver and adrenal glands. A CT scan of the brain was performed when clinically indicated (e.g. symptomatic patients or in order to demonstrate clinical remission of brain metastasis after cranial radiotherapy). Medical history, physical examination and blood cell count, including differential white blood cell (WBC) count, were repeated weekly.

Patients received intravenous (i.v.) vinorelbine over 10 min (immediately followed by 250 ml normal saline in order to avoid severe thrombophlebitis) and i.v. gemcitabine over 30 min on days 1, 8 and 15, with standard anti-emetics at the physician's decision. This treatment cycle was repeated on day 29 (= day 1 of the following cycle).

The starting doses of vinorelbine and gemcitabine were 10 mg/m^2 and 600 mg/m^2, respectively. Both drugs were then escalated according to a pre-established schedule (Table 1) and according to the toxicities observed. The dose-limiting toxicity with regard to myelosuppression was defined as follows: WBC $< 1.5\times10^9$/l on day 8, $< 1.0\times10^9$/l on day 15 or $< 3.0\times10^9$/l on day 29; WBC $< 1.0\times10^9$/l with fever $> 38.5^\circ$C; platelet count $< 50\,000\times10^9$/l on day 8 or 15, or $< 100\,000\times10^9$/l on day 29. Other dose-limiting toxicities were any toxicities WHO grade 3–4 (except alopecia WHO grade 3–4 and nausea/vomiting WHO grade 3).

A minimum of 3 patients completing two treatment cycles (except in case of dose-limiting toxicity) were required at each dose level. Once a dose-limiting toxicity had occurred in 1 of these 3 patients, additional patients, up to a maximum of 6, either completing two cycles or experiencing dose-limiting toxicity during the first two cycles, were entered. The maximum tolerated dose was defined as the dose one level below the level that resulted in dose-limiting toxicity in 2 or more patients.

Response evaluation according to standard criteria [14] was carried out after two 2 cycles and/or at any time when disease progression was clinically suspected. Progressive disease led to discontinuation of treatment.

RESULTS

40 previously untreated patients (9 female, 31 male), aged 35–75 years (median 62 years), with advanced NSCLC (11 IIIB, 29 IV; 25 adeno-, 13 squamous cell and 2 large cell carcinomas) and good performance status (2 Karnofsky 100%, 16 Karnofsky 90%, 13 Karnofsky 80%, 9 Karnofsky 70%) were admitted to this trial.

For each dose level, the drug doses, the number of patients entered and the number of treatment cycles are shown in Table 1. A total of 63 cycles were administered. 27 patients completed two cycles, whereas the remaining 13 patients received less than two cycles due to dose-limiting toxicity ($n = 3$), progressive disease ($n = 4$), patient's refusal ($n = 2$) and physician's decision ($n = 4$). Because of a lack of toxicity in dose level 1, dose level 2 was omitted. No dose-limiting toxicities were seen at dose levels 1–5. At dose level 6, 1 patient developed leucopenia WHO grade 4, thrombocytopenia WHO grade 4, nausea/vomiting and subsequent heart failure after having received treatment on days 1 and 8 of the first cycle. At dose level 7, pulmonary embolism was diagnosed in 1 patient on day 22 of the second treatment cycle, but was not considered as a dose-limiting toxicity. At dose level 8, dose-limiting toxicities were seen in 2 patients on day 15 of the first cycle. They included leucopenia WHO grade 4 and thrombocytopenia WHO grade 3 in 1 patient and stomatitis WHO grade 3 in another patient. Thus, the maximum tolerated dose was established at vinorelbine 25 mg/m^2 combined with 1,200 mg/m^2 gemcitabine on days 1, 8 and 15.

All patients receiving at least one dose of chemotherapy were eligible for toxicity evaluation. Haematological toxicity (Tables 2 and 3) included leucopenia in 55%, neutropenia in 48% and thrombocytopenia in 23% of all patients. Severe leucopenia occurred at dose level 6 (3 patients WHO grade 3, 1 patient WHO grade 4), level 7 (3 patients WHO grade 3) and level 8 (1 patient WHO grade 3, 1 patient WHO grade 4). Severe neutropenia occurred at dose level 6 in 3 patients (WHO grade 4), at dose level 7 in 2 patients (WHO grade 3) and at dose level 8 in 4 patients (2 patients WHO grade 3, 2 patients WHO grade 4). Usually, neutropenia was most pronounced on day 21. However, no episode of neutropenic fever occurred. Severe thrombocytopenia was seen at dose level 6 in 1 patient (WHO grade 4) and at dose level 8 in 1 patient (WHO grade 3). Anaemia occurred in 68% of all patients, but was tolerable because red blood cell transfusions were allowed in the case of severe anaemia.

Non-haematological toxicities are listed in Table 3. Mild nausea occurred in 28% and vomiting in 20% of all patients. 3 patients, all at dose levels 6–7, reported vomiting WHO grade 3. Skin toxicity and mucositis was seen in 43% of all patients and included exanthema in 9 patients, which was probably due to gemcitabine. Exanthema disappeared after

Table 1. *Dose escalation scheme, dose-limiting toxicity (DLT) and response*

Dose level	Vinorelbine (mg/m^2)	Gemcitabine (mg/m^2)	Total no. of patients	No. of patients with two cycles or DLT*	No. of cycles	No. of patients with DLT	Response†
1	10	600	4	3	6.6	0	0/4
2‡	15	600	–	–	–	–	–
3	15	800	5	3	7.6	0	0/5
4	20	800	4	3	7.3	0	1/3
5	20	1000	3	3	6.0	0	2/3
6	25	1000	8	6	11.3	1	3/5
7	25	1200	9	6	14.0	0	0/6
8	30	1200	7	6	10.3	2	1/5

*All patients completing either two cycles or experiencing dose limiting toxicity (DLT) within the first two cycles. †n of responding patients/n of patients evaluable for response. ‡Because of a lack of toxicity at dose level 1, dose level 2 was omitted.

Table 2. Haematological toxicity

	Dose level						
	1	3	4	5	6	7	8
Nadir WBC ($\times 10^9$/l)*							
Mean	4.5	6.6	4.4	2.7	2.4	3.4	2.7
Range	3.2–5.8	3.9–8.9	3.6–5.3	2.2–3.2	0.7–6.4	1.3–5.9	0.7–6.5
Nadir absolute neutrophil count ($\times 10^9$/l)*							
Mean	3.4	4.6	2.9	1.3	1.3	1.8	1.6
Range	1.5–4.7	2.1–7.5	1.8–4.3	1.1–1.6	0.3–3.8	0.6–3.1	0.1–4.6
Nadir platelet count ($\times 10^9$/l)*							
Mean	135	203	207	120	148	149	112
Range	91–160	100–287	131–312	72–200	17–223	84–209	41–166
Nadir Hb (mg/dl)*							
Mean	10.1	9.1	10.0	10.0	10.0	10.8	9.3
Range	8.5–12.0	8.1–10.5	8.2–11.3	9.1–10.6	9.0–11.4	9.1–13.1	7.6–11.8

*Worst results at any time for all entered patients are shown. WBC, white blood cells; Hb, haemoglobin.

Table 3. Toxicity according to WHO criteria

	Dose levels														
	1 ($n=4$)		3 ($n=5$)		4 ($n=4$)		5 ($n=3$)		6 ($n=8$)		7 ($n=9$)		8 ($n=7$)		All ($n=40$)
WHO grade	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–4
Leucopenia	1	0	1	0	2	0	3	0	2	4	0	3	4	2	22 (55%)
Neutropenia	1	0	0	0	1	0	3	0	3	3	2	2	0	4	19 (48%)
Haemoglobin	3	0	4	0	2	0	2	0	5	0	6	0	4	1	27 (68%)
Thrombocytopenia	1	0	0	0	0	0	3	0	1	1	2	0	0	1	9 (23%)
Increased AST	1	0	0	0	1	0	0	0	2	0	0	0	2	0	6 (15%)
Increased ALT	0	0	0	0	1	0	2	0	3	0	3	0	1	0	10 (25%)
Increased AP	0	0	3	1	4	0	2	0	2	0	2	0	2	0	17 (43%)
Proteinuria	0	0	0	0	0	0	1	0	1	0	0	0	1	0	3 (8%)
Flu-like symptoms	0	0	2	0	1	0	1	0	3	0	4	0	2	0	13 (33%)
Skin rash/mucositis	1	0	0	0	2	0	1	0	4	0	4	0	4	1	17 (43%)
Neurotoxicity	1	0	1	0	0	0	0	0	2	0	1	0	1	0	6 (15%)
Nausea and vomiting	1	0	2	0	2	0	3	0	1	1	1	2	6	0	19 (48%)
Alopecia	0	1	3	1	3	1	3	0	2	1	2	1	0	0	18 (45%)

No cases of increased creatine levels were observed at any dose level. AST, asparate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase.

treatment with corticosteroids and, due to the physician's decision, did result in discontinuation of treatment in 1 patient. Thrombophlebitis was seen in 5 patients. Mild flu-like symptoms were observed in 33% of all patients. Mild neurotoxicity, usually mild motoric weakness in the upper legs, was observed in 15% of all patients. Mild alopecia was seen in 45% of all patients. Slight elevation of liver enzymes was observed, predominantly at the higher dose levels. No renal toxicity was seen.

31 patients were evaluable for response. These patients included those receiving at least two treatment cycles (27 patients) and those progressing before completing two cycles (4 patients). 9 patients were not evaluable because of either occurrence of dose-limiting toxicity ($n=3$), the patient's refusal to complete two cycles ($n=2$) or the physician's decision to stop treatment before completing two cycles ($n=4$). One complete response (at dose level 5) and 6 partial responses were seen (Table 1). Thus, the overall response rate was 23%. Stable disease and progressive disease were documented in 14 (45%) and 10 (32%) patients, respectively. When only patients of dose levels 4–8 were analysed (22 patients), the response rate was 32%.

DISCUSSION

In the present phase I trial of vinorelbine/gemcitabine, the maximum tolerated dose was established at 25 mg/m^2 vinorelbine combined with 1200 mg/m^2 gemcitabine on days 1, 8 and 15 of a 4-week cycle. The dose-limiting toxicities were leucopenia plus thrombocytopenia in 2 patients and stomatitis in 1 patient. Dose-limiting haematotoxicity was expected because, in previous single agent phase I trials, the dose-limiting toxicities for vinorelbine were leucopenia as well as neutropenia [11], and the dose-limiting toxicities for gemcitabine were thrombocytopenia plus anaemia [12] and, at higher doses, additional neutropenia plus elevation of liver enzymes [13].

Frequent side-effects were leucopenia, anaemia, flu-like symptoms, slight elevation of liver enzymes and skin rash/mucositis (Table 3). The neutrophil nadir count decreased with increasing dose levels. Neutropenia WHO grade 3–4 occurred in 9/40 (23%) of all patients, particularly after day 15, but did not result in septicaemia. At dose levels 6–8, leucopenia WHO grade 3–4 and neutropenia WHO grade 3–4 occurred in approximately 30–50% and 22–60% of patients, respectively (Table 3). These frequencies are similar

to those reported from phase II trials for vinorelbine [4–6], but slightly higher than those reported for gemcitabine [7–10]. Other side-effects, including nausea/vomiting, neurotoxicity and alopecia, were only mild and did not result in any clinically significant problems.

Responses were seen at several dose levels, indicating a wide margin of efficacy of this protocol (Table 1). The fact that responses occurred at lower dose levels suggests that both scheduling of these cell cycle-specific drugs and absolute drug doses are important for efficacy.

The recommended doses for phase II trials are 20–25 mg/m^2 vinorelbine combined with 1,000–1,200 mg/m^2 gemcitabine. Myelotoxicity will have to be carefully monitored, and might require dose modifications and/or administration of haematoipoetic growth factors, particularly on day 15 and thereafter, as well as with increasing numbers of treatment cycles. Preliminary analysis [15] of our ongoing phase II trial with 25 mg/m^2 vinorelbine plus 1,200 mg/m^2 gemcitabine revealed leucopenia WHO grade 3–4 in approximately 50% of patients.

The advantages of vinorelbine/gemcitabine in comparison with cisplatin-based regimens are easy administration on an out-patient basis, better tolerability and lack of the necessity of hydration. However, it remains to be seen whether the activity of this combination with regard to response rate, survival and quality of life will be comparable with those of cisplatin-based protocols in patients with advanced NSCLC.

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