Pergamon

European Journal of Cancer, Vol. 35, No. 10, pp. 1457–1461, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00147-1

Original Paper

Ifosfamide, Vinorelbine and Gemcitabine in Advanced Non-small Cell Lung Cancer. A Phase I Study

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The objective of this phase I study was to identify the maximum tolerated dose (MTD) and toxicity of a three drug, platinum-free regimen, including gemcitabine, ifosfamide and vinorelbine, in the treatment of patients with advanced non-small cell lung cancer (NSCLC). 33 chemotherapy-naïve patients with histologically confirmed, unresectable NSCLC, received fixed doses of ifosfamide (1500 mg/m^2 days 1–3 with mesna) and vinorelbine (25 mg/m^2 days 3 and 8). The gemcitabine dose was escalated from 500 to 1200 mg/m^2 on days 3 and 8 every third week. The escalation was stopped at dose level 4 (gemcitabine 1200 mg/m^2) since all 3 patients of this cohort showed dose-limiting thrombocytopenia and/or neutropenia at treatment cycle 1. The dose recommended for phase II trials is: gemcitabine 1000 mg/m^2 and vinorelbine 25 mg/m^2 given on days 3 and 8 plus ifosfamide 1500 mg/m^2 on days 1–3. An encouraging response rate of 50% (95% confidence interval (CI): 32–68%) was observed in 32 patients evaluated. Our results show that ifosfamide, vinorelbine and gemcitabine can be safely administered as outpatient chemotherapy for NSCLC. Myelosuppression is the dose-limiting toxicity (DLT) of this regimen with no major subjective side-effects observed. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: advanced non-small cell lung cancer, chemotherapy, gemcitabine, ifosfamide, vinorelbine
Eur J Cancer, Vol. 35, No. 10, pp. 1457–1461, 1999

INTRODUCTION

NON-SMALL CELL lung cancer (NSCLC) accounts for more deaths in developed countries than any other male or female cancer [1]. Surgery may be curative at an early stage, but more than 75% of patients present with locally advanced or metastatic disease. These patients have a grim prognosis, with an expected survival time of approximately 4–6 months [1]. Although it has been demonstrated that chemotherapy can achieve a survival benefit compared with the best supportive care [2], treatment of stage III-B and stage IV NSCLC patients remains sub-optimal.

Cisplatin-based combination chemotherapy is currently considered as the most active treatment [3] for advanced NSCLC. A recent meta-analysis of 8 randomised trials comparing best supportive care with a cisplatin-based chemotherapy showed a modest (10%) but definite survival benefit over a 1 year period [2]. Moreover, another meta-analysis demonstrated that combination chemotherapy increased objective response and toxicity rates compared with single agent chemotherapy [4]. However, there is no consensus on a specific reference regimen for NSCLC.

Despite improved supportive measures, side-effects including nephrotoxicity, ototoxicity and cumulative myelosuppression often complicate cisplatin chemotherapy and limit its administration to four to six cycles [5]. Moreover, cisplatin toxicity may be higher in the elderly who represent the majority of NSCLC patients. For all these reasons, less toxic and more active treatments are required for NSCLC. Our interest, therefore, focused on outpatient treatments that decrease hospitalisation-related stress and expense. Searching for a novel active drug combination, gemcitabine, ifosfamide and vinorelbine were selected for their activity in NSCLC, their different mechanisms of action and different toxicity profiles.

Gemcitabine (2′-deoxy-2′, 2′-difluoroxycytidine monohydrochloride) is a new anticancer drug that exhibits a novel mechanism of action and high tolerability. It exhibits *in vitro* a wider spectrum of activity than its parent compound cytarabine

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Received 8 Feb. 1999; revised 4 May 1999; accepted 6 Jun. 1999.

[6] and when used as single agent in several phase II trials it produced a response rate greater than 20% in NSCLC patients, with a median survival exceeding 8 months [7–9]. Ifosfamide, an alkylating agent active against NSCLC [10] exhibits a greater activity than its parent compound cyclophosphamide on a variety of cell lines, including Lewis lung carcinoma cells [11]. Phase II studies using ifosfamide as a single agent have shown response rates ranging from 12 to 38% in NSCLC patients [12]. Vinorelbine, a new semisynthetic vinca alkaloid, exerts its biological activity by inhibiting microtubule assembly. It has been shown to act, *in vitro*, on a wide variety of cell lines, including NSCLC [13]. Early phase II and randomised studies have given response rates of 29% [14] and 28% [15] for vinorelbine when used as a single agent in the treatment of NSCLC.

Previously we have reported that the combination of carboplatin, ifosfamide and vinorelbine is highly effective [16] as an outpatient treatment of NSCLC. We therefore extended our research initiating a phase I study aimed to determine the MTD (maximum tolerated dose), the dose-limiting toxicities (DLTs) and the toxicity profile of gemcitabine, in combination with fixed doses of ifosfamide and vinorelbine [16] in NSCLC patients not previously treated.

PATIENTS AND METHODS

Chemotherapy-naïve patients with histologically or cytologically confirmed stage IIIB or IV NSCLC were entered in this phase I study. Other eligibility criteria included: bidimensionally measurable or assessable disease, age $\leq$75 years, performance status $\leq$3 (ECOG scale) and an anticipated life expectancy of at least 3 months. The patients were required to have an adequate haematological, hepatic, renal and cardiac function. No prior chemotherapy or thoracic radiotherapy was permitted. Patients with additional malignancies, other than curatively treated skin and cervical cancer, or with active cardiovascular disease were excluded.

Patients with a performance status of 3, untreated brain metastases and a life expectancy longer than 3 months were included in this trial, in order to make results of the trial more applicable to a broader population of lung cancer patients [17]. The study was approved by the local ethical committee and written informed consent was obtained from each patient.

Pretreatment evaluation included a medical history, clinical examination, complete blood cell count, determination of plasma urea and creatinine levels, a 24-h creatinine clearance, electrolyte measurement, a liver function test and serum carcinoembryonic antigen determination. Electrocardiogram, computed tomographic (CT) scan of chest and upper abdomen and X-rays of abnormal areas of bone scan uptake were performed. CT scan was used to evaluate hepatic lesions. Before each subsequent course of treatment all patients had a further blood cell count, plasma urea, electrolytes, serum creatinine, aspartate aminotransferase (ALT), alanine aminotransferase (AST), alkaline phosphatase (AP) and bilirubin measurement. In addition, a blood cell count was repeated weekly. Clinical tumour response and toxicity assessment were performed before each course of chemotherapy. Films or scans to document the response during therapy were repeated every three courses of chemotherapy or sooner if the patient appeared to have disease progression.

Outpatient treatment consisted of a fixed dose of ifosfamide and vinorelbine [16]. Ifosfamide 1500 mg/m^2 was diluted in 500 ml normal saline and delivered as a 1-h intravenous infusion on days 1, 2 and 3, along with 300 mg/m^2 of mesna that was repeated, 400 mg/m^2, orally at 4, 8 and 12 h after therapy. Vinorelbine was given 25 mg/m^2 by short intravenous (i.v.) infusion on days 3 and 8. Gemcitabine, administered over 30 min on days 3 and 8, was escalated from 500 to 800, 1000 and 1200 mg/m^2. The scheduled administration of gemcitabine on day 8 was in order to be able to recycle therapy every three weeks.

This schedule was designed to synergise maximally the mechanisms of action of the three drugs. Thus, the alkylating agent ifosfamide administered on days 1 to 3, which damages cells by DNA alkylation and consequently stimulates DNA synthesis and mitosis would synergise with gemcitabine and vinorelbine administered on days 3 and 8, which exhibit elevated activity on the dividing cells.

At least 10 patients were enrolled in each cohort and dose escalation was stopped if 30% or more patients, of a given cohort, exhibited DLT in the first treatment cycle [18]. DLT was defined as grade 4 neutropenia persisting for more than 7 days or grade 4 thrombocytopenia or grade 4 non-haematological toxicity (except for nausea or alopecia). A delay longer than 1 week in administering the second cycle of therapy was also considered DLT. There was no intrapatient dose escalation. Although this study was designed to evaluate toxicity, patients were assessed for response after three courses of therapy. An additional three therapeutic cycles were administered if patients showed a partial or complete response, according to World Health Organisation (WHO) response criteria. Patients exhibiting evidence of disease progression after two courses of chemotherapy were excluded from this study.

RESULTS

The characteristics of the 33 patients (27 males and 6 females with a median age of 66 years) entered in this study from September 1996 to November 1998, who received at least one course of treatment, are shown in Table 1. The median number of courses administered per patient was four (range: one to six courses).

The major toxicities encountered in this study were neutropenia and thrombocytopenia. No treatment-related death was observed. 10 patients were entered at the first dose level (gemcitabine 500 mg/m^2) and 37 courses of chemotherapy were evaluated (Tables 2 and 3). Neutropenia grade 4 was observed in 2 patients with 1 developing grade 4 thrombocytopenia. One patient with colon diverticulosis developed a bleeding rectal ulcer after the first course of chemotherapy. Of the 10 patients entered at the dose level two (800 mg/m^2 gemcitabine), 2 developed grade 4 neutropenia and 1 also developed grade 4 thrombocytopenia. Of 10 patients receiving gemcitabine 1000 mg/m^2, 5 developed grade 4 neutropenia and 1 of them also developed grade 4 thrombocytopenia at the fourth course of chemotherapy.

All 3 patients entered at level 4 developed grade 4 toxicity characterised by neutropenia and thrombocytopenia. In the subsequent chemotherapy courses administered to these patients drug doses were reduced by 20%.

The median white blood cell count (WBC) and platelet nadir occurred on day 14 (range 4–18), with a median haematological recovery observed by day 21. Neutropenic fever requiring hospitalisation was observed in 4 patients. The use of granulocyte colony-stimulating factor was not allowed in

Table 1. *Characteristics of patients*

Characteristics	*n* (%)
Patients	
Entered	33 (100)
Evaluable for toxicity	33 (100)
Evaluable for response	32 (97)
Sex	
Males	27 (82)
Females	6 (18)
Age	
Median (range)	66 (35–74) years
Performance status (ECOG)	
0–1	21 (64)
2	8 (24)
3	4 (12)
Stage	
IIIB	11 (33)
IV	22 (67)
Histology	
Squamous	18 (55)
Poorly-differentiated squamous	8 (24)
Adenocarcinoma	6 (18)
Large cell	1 (3)
Metastatic sites*	
Brain	11 (33)
Bones	8 (24)
Adrenals	5 (15)
Liver	4 (12)
Controlateral lung	3 (9)

*9 patients had more than one metastatic site.

this study. Various grades of anaemia were observed in 18 patients; and was treated with erythropoietin. Only 2 patients required blood transfusion for haemoglobin value <7 g/100 ml. Five courses of chemotherapy (4.4%) were delayed for 1 week due to myelosuppression. The dose intensity administered for ifosfamide and vinorelbine, for all patients was 96.21% and 95.8%, respectively. Non-haematological toxicity was minimal. Nausea and vomiting were severe (grade 3) in only 12 patients (37%), due to the appropriate administration of $5HT_3$ antagonists and dexamethasone. Grade 3 alopecia occurred in 72% of patients and was not prevented by head hypothermia. 9 patients (28%) exhibited a transient elevation in the concentration of liver enzymes.

Response and survival

Although response to therapy was not the end-point of this study, patients who had completed at least three cycles of chemotherapy were evaluated for response on an intent-to-treat basis. Of 33 patients evaluated for toxicity, 32 were evaluated for response. One patient who has just completed the first course of chemotherapy was evaluated for toxicity only. Objective overall remission was observed in 16 patients (response rate 50%, 95% confidence interval (CI): 32–68%). A complete or partial response was observed in 2 (6%) and 14 (44%) patients, respectively. Disease was stable in 13 (41%) patients and had progressed in 3 (9%) patients. Median time to disease progression was 8.5 months (range $2+-27.1+$); median overall survival was 10.2 months (range $2+-27.1+$). The 1-year survival rate was 46%. By December 1998, 12 patients (37.5%) remained alive and 9 (28%) were progression-free between 2 and 27 months after initiating treatment. 2 patients with a stage IIIB (poorly differentiated squamous cell carcinoma with controlateral mediastinal nodes and adenocarcinoma with cytology-positive pleural effusion) underwent right pleuropneumonectomy and left upper lobectomy, respectively, after three courses of chemotherapy. Pathological examination of the specimen showed no viable tumour cells after chemotherapy. These 2 patients received three further courses of chemotherapy after surgery and remained in complete remission after 27 and 23 months, respectively.

14 patients that had a response or stable disease with gemcitabine/vinorelbine/ifosfamide were treated, when they progressed with carboplatin/etoposide salvage chemotherapy: 9 responses were observed. Of the 11 patients that had brain metastases, 6 achieved a partial response, 4 were stable and 1 progressed. Performance status improved in 19 patients (59%).

DISCUSSION

The evolving knowledge and availability of novel drugs has stimulated the analysis of new cisplatin-free drug combinations in order to improve survival, reduce drug-induced toxicity and permit administration to outpatients. In a previous

Table 2. *Toxicity according to WHO criteria (number of patients shown)*

	WHO grade (%)							
	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4
GEM mg/m^2	500	500	800	800	1000	1000	1200	1200
n pts	10	10	10	10	10	10	3	3
Leucopenia	5 (50)	4 (40)	4 (40)	4 (40)	2 (20)	6 (60)		2 (66)
Neutropenia	5 (50)	3 (30)	2 (20)	6 (60)		8 (80)		2 (66)
Haemoglobin	6 (60)		4 (40)	1 (10)	3 (30)	1 (10)	1 (33)	2 (66)
Thrombocytopenia	4 (40)	1 (10)	3 (30)	1 (10)	2 (20)	2 (20)		3 (100)
Increased AST	3 (30)		1 (10)		2 (20)			
Increased ALT	3 (30)		2 (20)		2 (20)			
Increased AP	4 (40)		3 (30)		2 (20)			
Proteinuria							1 (33)	
Flu-like symptoms			1 (10)		2 (20)		1 (33)	1 (33)
Skin rash/mucositis		1 (10)			2 (20)			
Neurotoxicity								
Nausea and vomiting	2 (20)	3 (30)	1 (10)	2 (20)	3 (30)	5 (50)		2 (66)
Alopecia	5 (50)	5 (50)	3 (30)	7 (70)	1 (10)	9 (90)		2 (66)

GEM, gemcitabine; AST, alanine aminotransferase; ALT, aspartate aminotransferase; AP, alkaline phosphatase.

Table 3. Dose escalation scheme, dose-limiting toxicity, dose intensity and response

Dose level of gemcitabine	*n* Pts	Cycles	DLT (*n* Pts)	Type	DI	Response
500 mg/m^2	10	37	2	2 neutropenia, 1 thrombocytopenia	333	4/10
800 mg/m^2	10	37	2	2 neutropenia, 1 thrombocytopenia	533	5/10
1000 mg/m^2	10	32	5	5 neutropenia, 1 thrombocytopenia	666	6/10
1200 mg/m^2	3	8	3	2 neutropenia, 3 thrombocytopenia	800	1/2
Total	33	113	12	RR 50% (95% CI: 32–68%)		

DLT, dose-limiting toxicity; DI, dose intensity (mg/m^2/week); RR, response rate; CI, confidence interval.

study [16], we reported that vinorelbine and ifosfamide combined with carboplatin, have activity in the treatment of NSCLC, achieving a response rate up to 45%, with 1-year survival rate approaching 48%. However, haematological toxicity occurred in 60% of the 247 treatment cycles administered with 14 episodes of febrile neutropenia that required hospitalisation. In two phase II randomised trials, single agent gemcitabine has shown similar response and survival rates compared with the cisplatin + etoposide combination with decreased toxicity [19, 20]. We, therefore, designed a phase I study aimed at finding the dose of gemcitabine which could substitute for carboplatin of the previous study in the treatment of NSCLC.

Our results indicate that the MTD of gemcitabine is 1200 mg/m^2 delivered on days 3 and 8 of the treatment cycle, combined with vinorelbine 25 mg/m^2 delivered on the same days and ifosfamide 1500 mg/m^2 given from day 1 to day 3. The recommended dose of gemcitabine for phase II trials is 1000 mg/m^2 administered on days 3 and 8 combined with the abovementioned doses of ifosfamide and vinorelbine.

As expected, myelosuppression was the DLT. The activity of this platinum-free regimen was encouraging, with 2 patients exhibiting a complete pathological response. Responses were also observed at all dose levels (Table 3), indicating a wide margin of activity for this regimen. This regimen was successfully administered to 4 patients with a performance status of 3. One of these patients had a significant partial response of the pulmonary lymphangitis and of the brain metastases, with a considerable improvement of his dyspnoea and performance status.

The main advantage of combining gemcitabine/vinorelbine/ifosfamide over cisplatin-based regimens is the possibility that this regimen can be administered on an outpatient basis and avoids volume overload that often has contraindications in the elderly who represent most of the NSCLC population. In addition, a further advantage of this regimen is the possibility of administering a platinum-containing regimen as salvage chemotherapy in patients with resistant malignancies.

Since neutropenia appears as the main side-effect, it may be possible to administer higher doses of gemcitabine supported by haematopoietic growth factors. In fact, non-haematological toxicity was generally mild and was not dose limiting in this study. The weekly dose intensity of ifosfamide and vinorelbine for all patients was 1500 mg/m^2 and 17 mg/m^2, respectively. The weekly dose intensity of gemcitabine was for each of the four levels 333 mg/m^2, 533 mg/m^2, 666 mg/m^2, 800 mg/m^2, respectively. The doses actually achieved for ifosfamide and vinorelbine were 96.21% and 95.8% of the initial dose, respectively, and for gemcitabine, taking account of all chemotherapy courses were 97.25%, 98.57%, 89.3% and 80%, respectively compared with the initial dose delivered. At all dose levels the actual gemcitabine dose achieved was 91% of the initial planned dose. In conclusion, we recommend a gemcitabine dose for phase II study of 1000 mg/m^2 that translates into a dose intensity of 666 mg/m^2/week, which is similar to the active dose reported by other authors [21]. However, we await a randomised trial to ascertain the value of this regimen compared with carboplatin, ifosfamide, paclitaxel combination chemotherapy.

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