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Gemcitabine plus vinorelbine for the treatment of advanced non-small cell lung cancer

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Abstract

The aim of this study was to determine the clinical activity and toxicity of a novel chemotherapy regimen of weekly gemcitabine and vinorelbine in patients with advanced non-small cell lung cancer (NSCLC). 40 chemotherapy-naïve patients with stage IIIB/IV NSCLC were included. The doses of gemcitabine and vinorelbine were 1000 and 25 mg/m^2, respectively, given on days 1, 8 and 15, every 28 days. 38 patients were evaluable for response. One patient achieved a complete response (CR) and 10 attained a partial response (PR), for an overall response rate (ORR) of 29% (95% confidence interval (CI): 15–43%). 47% of patients experienced a clinical benefit. The main toxicity consisted of grade 3 anaemia and neutropenia in 5% of patients. Non-haematological toxicity was minimal. The dose-intensities were 744 mg/m^2/week for gemcitabine and 15 mg/m^2/week for vinorelbine. 40% of the patients survived for longer than 1 year. The median time to progression was 4 months and the median survival 8.5 months (95% CI: 3.1–13.8 months). The weekly administration of gemcitabine and vinorelbine is very well tolerated and results in an acceptable response rate for the treatment of NSCLC.

Keywords: Gemcitabine; Vinorelbine; Non-small cell lung cancer; Toxicity

1. Introduction

Lung cancer represents a major health problem in the Western World. It is the most common malignancy among men and its incidence is rapidly increasing in women [1]. Approximately 80% of new cases of lung cancer are non-small cell lung cancers (NSCLC) and over 70% of patients are diagnosed when the disease is advanced (stages IIIB and IV). Less than 5% of patients remain alive at 5 years. A meta-analysis showed that combination chemotherapy offers a modest, but significant, survival benefit of 1.5 months in patients with advanced NSCLC [2]. Most regimens of combination chemotherapy include cisplatin [3,4], although it causes renal, gastrointestinal and neurological toxicity.

Gemcitabine is a nucleoside antimetabolite analogue of deoxycytidine that is active against a range of solid tumours. Anderson and colleagues [5] reported a response rate of 20% and a median survival of 28 weeks with gemcitabine as first-line therapy for advanced NSCLC. They also observed a low toxicity and symptomatic relief in their patients. Vinorelbine is a vinca alkaloid that produced a 29% response rate and a median survival of 32 weeks in a large French trial [6]. Synergism of gemcitabine and vinorelbine has been proposed [7]. Based on these data, we performed a phase II trial with a new schedule of gemcitabine and vinorelbine.

2. Patients and methods

From January 1997 to October 1998, 40 consecutive patients were included in this phase II study. Eligibility criteria were as follows: (1) histologically confirmed NSCLC; (2) either stage IIIB with no option for radical treatment, or stage IV disease; (3) performance status World Health Organization (WHO) scale 0 to 2; (4) adequate bone marrow reserve, i.e. a neutrophil count $>1500\times10^6$/l, haemoglobin >100 g/l, platelets $>100\times10^9$/l; (5) adequate liver (total bilirubin <25.65 μmol/l, alanine aminotransferase (ALAT)/asparate aminotransferase (ASAT) $\leqslant 3$ times the upper normal limit) and renal function (serum creatinine <176.8

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μmol/l); (6) no previous chemotherapy; (7) measurable disease by computed tomography (CT) scan. Pleural effusion, ascites, osteoblastic lesions and lesions in areas previously treated with radiotherapy were not considered as measurable disease. Exclusion criteria were: (1) presence of leukaemia or another primary tumour (except basal cell carcinoma or stage I squamous-cell cervical carcinoma adequately treated); central nervous system (CNS) metastases; significant concomitant diseases, such as cardiac failure requiring therapy, or neurological or psychiatric disorders. All patients gave informed consent. Pretreatment evaluation included a complete history and physical examination, including baseline weight and pain assessment (Pain Assessment Card, ranging from 0 = no pain, to 10), liver and renal function tests, a bronchoscopy, chest X-ray films, and chest and abdominal CT scans. Complete blood counts were performed every week.

Chemotherapy consisted of gemcitabine 1000 mg/m^2 diluted in 500 ml of normal saline, followed by bolus vinorelbine 25 mg/m^2, both on days 1, 8 and 15, every 28 days. All patients received metoclopramide 30 mg as antiemetic therapy. Dose adjustment was based on leucocyte and platelet counts performed on the day of treatment. In the case of WHO grade 3 leucopenia or grade 1–2 thrombocytopenia, doses were reduced by 25%. In the case of grade 4 leucopenia or grade 3–4 thrombocytopenia, therapy was withheld until recovery, and doses were reduced by 25% in the following courses. Treatment was continued until progression or the appearance of intolerable toxicity. A CT scan was performed every 8 weeks. WHO guidelines were used to assess response and toxicity.

The Flemming method was used to determine sample size. Survival and time to progression were calculated from the start of therapy by using the Kaplan–Meier method. Clinical benefit was also assessed according to the issue by Burris and colleagues [8] and included analgesic consumption, body weight and WHO performance status. The change was positive if there was $\geqslant 50\%$ decrease in analgesic consumption (weekly morphine-equivalent mg), an improvement of 1 point on the performance status, or a weight gain $\geqslant 5\%$ (excluding third-space fluid). Clinical benefit was defined as an improvement in at least one of these parameters without worsening of the others for >4 weeks.

3. Results

40 patients were included, all evaluable for toxicity. 38 were also evaluable for response. 2 patients died of complications non-related to the treatment, 1 due to a digestive haemorrhage and the other due to a respiratory infection. Table 1 shows the patients' characteristics.

A total of 147 cycles were given, with a median of four per patient (range 1–7). The mean dose intensities were 744 mg/m^2/week for gemcitabine and 15 mg/m^2/week for vinorelbine, which corresponds to 99 and 82% of the planned doses, respectively. In 10 patients, doses were reduced because of haematological toxicity. 5 patients required vinorelbine dose reduction because of peripheral neuropathy. In 4 patients, the treatment was delayed for comorbidities (3 infectious disease and 1 diabetes hiperosmolar status).

There was one complete response (CR) and 10 partial responses (PR), for an overall response rate (ORR) of 29% (95% confidence interval (CI): 15–43%). The CR complete response was evaluated by performing a CT scan and a bronchoscopy (this patient subsequently received thoracic radiotherapy). The disease remained stable in 12 patients (32%) and progressed in 15 (39%). Palliative radiotherapy to the brain was performed in 3 patients (8%), whereas 13 patients (33%) received second-line chemotherapy with cisplatin after progression. 40% of patients survived longer than 1 year. The median time to progression was 4 months and the median survival 8.5 months (95% CI: 3.1–13.8 months).

Chemotherapy was very well tolerated, the most significant toxicity being haematological. Grade 3

Table 1
Patients' characteristics

Characteristic	*n* (%)
Gender	
Male	38 (95)
Female	2 (5)
Age (years)	
Median (range)	60 (45–78)
WHO performance status	
0	2 (5)
1	29 (73)
2	9 (23)
Histology	
Squamous	24 (60)
Adenocarcinoma	11 (28)
Large cell	5 (13)
Stage	
IIIb	14 (35)
IV	26 (65)
Symptoms	
Three symptoms	12 (30)
Two symptoms	22 (55)
One symptom	6 (15)
Dyspnoea	20 (50)
Cough	17 (43)
Pain	16 (40)
Asthenia	9 (23)
Anorexia	8 (20)
Hoarseness	6 (15)
Haemoptysis	6 (15)

WHO, World Health Organization.

Table 2
Toxicity analysis, WHO grading, worst toxicity per patient

Side-effect	Grade			
	1 *n* (%)	2 *n* (%)	3 *n* (%)	4 *n* (%)
Anaemia	13 (33)	10 (25)	2 (5)	0
Neutropenia	9 (23)	1 (3)	2 (5)	0
Thrombocytopenia	5 (13)	2 (5)	1 (3)	0
Hepatic	0	0	0	0
Alopecia	5 (13)	0	0	0
Nausea/vomiting	8 (20)	4 (10)	0	0
Neurotoxicity	8 (20)	0	0	0
Renal toxicity	2 (5)	0	0	0
Diarrhoea	2 (5)	0	0	0
Mucositis	2 (5)	0	0	0

WHO, World Health Organization.

neutropenia and anaemia developed in 5% of patients. There were no toxic deaths. Table 2 shows the toxicity data. 18 out of 38 patients (47%) had a clinical benefit, usually within the first three courses of chemotherapy. Clinical benefit was assessed every treatment and monthly after chemotherapy. The median duration of the benefit and symptom relief was 6 months (range: 1.5–12 months). Dyspnoea improved in 6 out of 20 patients (30%), cough in 5 out of 17 (29%), pain in 6 out of 16 (38%) and asthenia/anorexia in 3 out of 9 (33%). Clinical benefit was observed in all the patients achieving an objective response, in 50% of those who had stable disease, and in 6% of those who had a progression.

4. Discussion

The response rate in this phase II study of gemcitabine and vinorelbine was 29%. Both the response rate and the survival were similar to those obtained with cisplatin-containing regimens, but with very low toxicity. However, our results must be interpreted with caution due to the small number of patients. Cisplatin combinations yield a response rate of approximately 31%, with a median survival in the range of 4.5–6.5 months. Schiller and colleagues [9] in a Eastern Cooperative Oncology Group (ECOG) randomised trial of four new chemotherapy schedules in advanced NSCLC reported a median survival around 7.4–8.1 months. Although cisplatin is usually recommended for the treatment of advanced NSCLC [4], it is difficult to administer and produces significant toxicity, which can decrease patients' quality of life. Some comparisons of regimens with or without cisplatin have been performed in the last years. Luedke and coworkers [10] reported no differences in the response rate or survival among 247 patients randomised to receive mitomycin-C plus vindesine or cisplatin plus vindesine. Gridelli and colleagues [11] compared mitomycin-C, vindesine and etoposide with mitomycin-C, vindesine and cisplatin in 204 patients with stage IV disease, and observed no differences in the response rate, survival and symptom palliation.

We decided to combine gemcitabine and vinorelbine because they are active in weekly schedules and do not have overlapping toxicities. Esteban and coworkers [12] have showed the feasibility of this combination, with gemcitabine at a dose of 1000 mg/m^2 and vinorelbine at 25–30 mg/m^2, both on days 1, 8 and 15, every 28 days. Lorusson and colleagues [13] administered the therapy on days 1 and 8 every 21 days in 49 patients: the response rate was 36%, and a clinical benefit was observed in 59% of patients. Isokangas and coworkers [14] used gemcitabine 1200 mg/m^2 and vinorelbine 35 mg/m^2, both on days 1 and 15, every 28 days in 28 patients with stage IIIB–IV disease: there were three CRs and 10 PRs (ORR 46%). In this study, 24% of patients had grade 3–4 neutropenia. The median survival was 8 months and the median time to progression 4 months. Frasci and colleagues [15] treated 70-year-old patients with stage IIIB or IV NSCLC. 120 eligible patients were randomised to receive gemcitabine 1200 mg/m^2 and vinorelbine 30 mg/m^2 on days 1 and 8 every 3 weeks or vinorelbine 30 mg/m^2 on days 1 and 8 every 3 weeks. The addition of gemcitabine to vinorelbine was associated with significantly better survival.

47% of our patients obtained a clinical benefit. This novel concept, although not well validated in the literature, has been supported by a number of authors [8,13,16,17]. We think that it is easier to perform than the assessment of quality of life, but it includes some parameters that are not very specific for lung tumours. As most patients with advanced NSCLC die of their disease, therapy must be directed to palliation. This means that cancer treatment should not add symptoms to those already present as a result of the tumour. The efficacy of chemotherapy should be measured in terms of improvement in quality of life and symptomatic relief. Highly toxic regimens have no place in the care of advanced incurable disease [18]. Thus, some of the new combinations for the treatment of advanced NSCLC try to improve quality of life and survival with the lowest toxicity possible.

In conclusion, this combination of gemcitabine and vinorelbine is active and very well tolerated for the treatment of patients with advanced NSCLC. Future studies could incorporate a third drug in an attempt to improve the results.

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