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Gemcitabine and vinorelbine as first-line chemotherapy for advanced non-small cell lung cancer: a phase II trial

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Abstract

The purpose of this phase II study was to investigate the efficacy and safety of gemcitabine plus vinorelbine as first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). Eligibility criteria included cytologically or histologically confirmed NSCLC (stage IIIB or IV), no previous chemotherapy, and bidimensionally measurable disease. Patients received 1000 mg/m^2 gemcitabine and 30 mg/m^2 vinorelbine on days 1, 8 and 15 every 4 weeks up to eight courses. From December 1997 to November 1998, 70 patients (59 stage IV and 11 stage IIIB disease), with a median age of 59 years (range 38–74 years) were enrolled. The intent-to-treat response rate was 41% (95% confidence interval (CI) 30–54%) with 1 complete responder (CR) and 28 partial responders (PRs), 15 patients had stable disease (SD) and 26 progressed (PD). Median survival was 8.3 months (95% CI 6.0–9.9 months), median progression-free survival (PFS) was 4.8 months (95% CI 3.9–5.5 months), and 1-year survival rate was 33.5% (95% CI 24.0–46.8%). Patients received a total of 229 cycles. Haematological and non-haematological toxicities were moderate. Transient World Health Organization (WHO)-grade IV leucopenia and thrombocytopenia occurred in 13 (6%) and two (1%) cycles, respectively. The predominant non-haematological toxicity was local reactions of the veins in 19 (27%) patients (WHO-grade II and III). Neurotoxicity was infrequent, non-cumulative, and reversible. The combination of gemcitabine and vinorelbine has demonstrated activity in metastatic NSCLC, with response and survival rates similar to those of cisplatin-based regimens and a more favourable toxicity profile that is well tolerated in an outpatient setting. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Chemotherapy; Gemcitabine; Non-small cell lung cancer; Phase II trial; Vinorelbine

1. Introduction

In Western Europe and the United States, lung cancer is the most frequent cause of death due to malignant tumours. Non-small cell lung cancer (NSCLC) accounts for more than 75% of pulmonary carcinomas. Treatment of patients with NSCLC is a particular challenge in oncology because more than one third of patients have distant metastases (stage IV) at diagnosis [1], allowing only palliative treatment. Median survival for these patients ranges between 3 and 6 months [2]. Compared with small-cell lung cancer, NSCLC is generally considered much less chemosensitive. Results with conventional cytotoxic drugs have been somewhat

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discouraging; only five agents — ifosfamide, vindesine, vinblastine, mitomycin, and cisplatin — have demonstrated a response rate greater than 15%, while conventional platinum-based combination regimens have resulted in response rates between 10 and 30% [3–5].

A recent meta-analysis indicates that chemotherapy significantly improves survival and symptom control compared with best supportive care in stage IV NCSLC patients [6]. Chemotherapy achieved a reduction in mortality, as well as an improvement in quality of life, particularly during the first 6 months of treatment [7]. Median survival time was prolonged from 16–17 to 28–35 weeks and 1-year survival rates increased from 10 to 20%, especially in those patients responding to chemotherapy. Analysis of single agents revealed that only cisplatin produces a significant benefit compared with best supportive care, whereas alkylating agents, vinca alkaloids and etoposide have no or only insignificant effect on survival [6]. However, the substantial toxicity of the cisplatin-containing regimens undermine their advantages in terms of survival and symptom control.

Thus, equally active, but better tolerated agents are needed to optimise therapy of metastatic and advanced NSCLC. Since the early 1990s, promising new active cytotoxic agents were investigated in advanced and metastatic NSCLC. These novel agents include: the vinca-alkaloid vinorelbine, the antimetabolite gemcitabine, the taxanes paclitaxel and docetaxel, the camptothecin-derivatives irinotecan and topotecan, and the benzotriazine-derivative tirapazamine.

The nucleoside analogue, gemcitabine (2′2′-difluorodeoxycytidine), is a pyrimidine-antimetabolite. Gemcitabine is a pro-drug that is transformed intracellularly by deoxycytidine kinase into its active metabolites diphosphate and triphosphate. When gemcitabine triphosphate is incorporated into DNA, it leads to chain termination and induces apoptosis. Following gemcitabine incorporation, one additional deoxynucleotide is incorporated into DNA. This 'masked chain termination' protects the gemcitabine nucleoside from mechanisms of repair. Gemcitabine is generally well tolerated, the most frequent side-effect being myelosuppression which is usually mild. Other uncommon side-effects include rashes, a flu-like syndrome, pulmonary toxicity and elevated transaminases [8].

Vinorelbine (5′-nor-anhydrovinblastine) is a semi-synthetic vinca-alkaloid. It binds to tubulin, the basic protein subunit of cellular microtubules, resulting in the inhibition of microtubule formation and thus disruption of the mitotic spindle apparatus during mitosis. The inhibitory effects on the polymerisation of mitotic microtubules are equal to those of the other vinca-alkaloids, but vinorelbine has less effect on axonal microtubules. The primary toxicities observed with vinorelbine are myelosuppression, phlebitis, and usually mild and reversible peripheral neuropathy [9].

Gemcitabine and vinorelbine are two of the most extensively evaluated new cytotoxic agents. The use of these agents has extended the therapeutic possibilities for the management of metastatic NSCLC. Each is characterised by very favourable toxicity profiles that are far better tolerated than platinum-based regimens, and have average single-agent response rates of 20% [10–13]. In a randomised phase III trial, vinorelbine alone had response and survival rates equal to those of a cisplatin and vindesine combination [14,15]. In addition, a combination regimen of cisplatin and etoposide showed no benefit compared with gemcitabine alone [16,17]. Phase I trials [18,19] and a pilot study [20] have observed that a combination of gemcitabine and vinorelbine is feasible. The results of one phase I trial showed that the maximum tolerated dose of gemcitabine in combination with 30 mg/m^2 vinorelbine was 1200 mg/m^2 [18]. In this phase I trial, gemcitabine and vinorelbine were given on days 1 and 8 in a 3-week cycle. In another phase I trial, the maximum tolerated dose for vinorelbine was 25 mg/m^2 and gemcitabine was 1200 mg/m^2 on days 1, 8 and 15 in a 4-week cycle [19]. In both studies, the dose-limiting toxicity was myelosuppression. In a pilot study, 12 patients received 30 mg/m^2 vinorelbine on days 1, 8, 15 and 22, and gemcitabine 1000 mg/m^2 on days 1, 8 and 15 of a 4-week cycle, in which 9 out of 12 patients suffered grade 3–4 neutropenia [20]. Based on the data from these three trials, we decided to use 1000 mg/m^2 gemcitabine and 30 mg/m^2 vinorelbine on days 1, 8 and 15 every 4 weeks. We established a dose-modification system to easily control haematotoxicity on days 8 and 15.

As yet, no adequate standard of chemotherapy exists for patients with NSCLC. Thus, in this phase II study, we evaluated the potential of gemcitabine and vinorelbine in combination as a first-line treatment in patients with metastatic NSCLC.

2. Patients and methods

Eligibility criteria included cytologically or histologically confirmed NSCLC (stage IIIB or IV), and no previous chemotherapeutic treatment. Patients were also required to have objective bidimensionally measurable ($\geqslant 10\times 10$ mm) disease which was outside previous radiotherapy fields, a life expectancy of at least 12 weeks, a performance status $\geqslant 70$ (Karnofsky Performance Scale (KPS)), age between 18 and 75 years, and adequate bone marrow (neutrophils $\geqslant 2.0\times 10^9$/l, platelets $\geqslant 100\times 10^9$/l), hepatic (bilirubin $\leqslant 1.5\times$upper normal limit (UNL) and alamine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leqslant 3\times$UNL in the absence of liver metastases or ALT and AST $\leqslant 5\times$UNL in the presence of liver metastases), and renal (serum creatinine $\leqslant 5\times$UNL) function. Patients with brain metastases were eligible as well.

Patients were excluded from the study if they had previous cancer (except adequately treated basal cell carcinoma of the skin or carcinoma of the cervix), pre-existing sensory or motor neuropathy greater than World Health Organization (WHO) grade I, a history of myocardial infarction, coronary heart disease greater than or equal to grade III (Canadian Cardiovascular Society scale), ventricular cardiac arrhythmias $\geqslant$grade IIIB (Lown scale), cardiac insufficiency $\geqslant$grade III (New York Heart Association scale) and active infections. Exclusion criteria also included pregnancy, breast feeding and inadequate contraceptive precautions. All eligible patients gave informed consent prior to entering this trial. The study was approved by the local ethic committee and by the protocol committee of the German Cancer Society.

2.1. Treatment schedule

Patients received 1000 mg/m^2 gemcitabine as a 30-min infusion followed 1 h later by 30 mg/m^2 vinorelbine as a 15-min infusion on days 1, 8 and 15 every 4 weeks in an outpatient setting. To protect the vein in which the vinorelbine was infused and prevent the development of phlebitis, 250 ml of 0.9% saline was infused immediately after vinorelbine. Both drugs were administered as intravenous (i.v.) infusions in 0.9% saline. A combination of metoclopramide and dexamethasone was given on days 1, 8 and 15, 15–30 min before starting chemotherapy to prevent nausea and vomiting. Patients received a maximum of eight courses.

Within courses, doses of gemcitabine and vinorelbine were modified as follows: no reduction for neutrophils $\geqslant 1.5\times10^9$/l and platelets $\geqslant 100\times10^9$/l; 50% dose reduction for neutrophils 1.0–1.49$\times10^9$/l or platelets 75–99$\times10^9$/l; dose delay for neutrophils $<1.0\times10^9$/l or platelets $<75\times10^9$/l. When haematological WHO-toxicity grade IV or non-haematological WHO-toxicity grade III (except for alopecia and nausea/vomiting) occurred at any time, a dose reduction of 25% was made for the subsequent cycles.

2.2. Treatment evaluation

Pretreatment evaluation included complete history and physical examination with evaluation of the performance status score, chest X-rays in anterior–posterior and lateral view, computed tomography (CT) scan of the chest, sonography or computed tomography of the upper abdomen, fibre optic bronchoscopy with bronchoaspirate and/or brushing and/or bronchial biopsy, complete blood cell count, and serum chemistry analysis. Brain CT scan and radionuclide bone scan were only performed if clinically indicated. All pretreatment imaging procedures were performed within 4 weeks of study entry. The physical examination with evaluation of the performance status score and chest X-ray were repeated every 4 weeks. The indicator lesion(s) were measured with CT scan after every two cycles and, in the event of response or stable disease, 4 weeks later to confirm the response/stable disease.

To detect acute haematological toxicity, blood cell count with differential was performed weekly, and chemistry analysis was performed at the beginning of each cycle. Non-haematological acute toxicity was assessed weekly. Toxicities were evaluated according to WHO criteria. Tumour response was assessed after two cycles of therapy according to standard WHO criteria.

Response rate, survival and toxicity was assessed for all enrolled patients on an intent-to-treat basis. Median progression-free survival (PFS) was calculated from the start of treatment to the first documented disease progression or death (whatever the reason of death). The Kaplan–Meier method was used to analyse median survival and median PFS.

3. Results

3.1. Patient characteristics

From December 1997 to November 1998, 70 patients were enrolled in the study. Patient characteristics are provided in Table 1. The majority of patients (79%) were men. Patients had a median age of 59 years (6 patients were $\geqslant$70 years), and a median Karnofsky performance status of 80. 11 (16%) patients presented with stage IIIB and 59 (84%) with stage IV disease at diagnosis. The predominant histological type, occurring in 29 patients (41%), was adenocarcinoma. Prior treatments included 12 (17%) patients with surgery, 2 (3%) with radiotherapy of the chest, and 2 (3%) with cranial irradiation. Only 2 patients had objective bidimensionally measurable disease of less than 20$\times$20 mm (1 patient 15$\times$20 mm, 1 patient 18$\times$18 mm).

3.2. Response and survival

There were one complete response (CR) and 28 partial responses (PR), accounting for an overall response rate for the intent-to-treat assessment ($n=70$) of 41% (95% confidence interval (CI) 30–54%). 15 patients had stable disease, and 26 patients progressed (Table 2). Median survival was 8.3 months (95% CI 6.0–9.9 months) (Fig. 1), median progression-free survival was 4.6 months (95% CI 3.9–5.5 months) (Fig. 2), and the 1-year survival rate was 33.5% (95% CI 24.0–46.8%).

3.3. Toxicity

Patients received a total of 229 cycles of gemcitabine and vinorelbine. The mean number of cycles per patient

was three (range 1–8 cycles). Within courses, 32 dose reductions according to the dose modification system occured on 32 treatment days. Eight days of therapy were omitted and 71 days of therapy were delayed (31% of all cycles). In the course of treatment for both drugs, a dose reduction up to 75% of the starting dose was necessary in 8 (11%) patients. Dose intensity was determined according to Hryniuk and colleagues [21]. Based on 229 treatment cycles, 24 days with reduction to 75%, 32 days with reduction to 50%, 8 days not given and 71 days delayed by a mean of 7 days, the average dose intensity regarding all cycles and patients was 704.4 mg/m^2/week of gemcitabine and 21.1 mg/m^2/week of vinorelbine given in combination. The predominant cause of dose reduction, as well as omissions and delays, was haematological toxicity, namely neutropenia and thrombocytopenia.

Haematological and non-haematological toxicities were moderate. WHO-grade IV leucopenia and thrombocytopenia were observed in 13 (6%) and 2 (1%) cycles (Table 3), as well as 7 (10%) and 2 (3%) patients (Table 4), respectively. 2 patients (3%) had one episode of febrile neutropenia. The duration of leucopenia and thrombocytopenia was brief, however, and no leucopenia-induced death occurred. The predominant non-haematological toxicity was local reactions of the veins (Table 5); 19 (27%) patients had WHO-grade II and III local reactions of the veins. Neurotoxicity was infrequent, non-cumulative, and reversible, with WHO-grade II and III neurotoxicity occurring in only 6 (9%) patients. Nausea and vomiting were manageable with metoclopramide and dexamethasone support (5-HT$_3$-antagonists were not necessary). Moderate-to-severe fatigue was observed in 8 patients (11%). Only 1 patient had alopecia (grade III).

Table 1
Patient characteristics

Characteristics	No. of patients (%)
Total no. of patients	70 (100)
Karnofsky PS	
100	9 (13)
90	16 (23)
80	26 (37)
70	19 (27)
Gender	
Male/female	55 (79)/15 (21)
Age (years)	
Median (range)	59 (38–74)
Stage	
IIIB	11 (16)
IV	59 (84)
Histology	
Adenocarcinoma	29 (41)
Squamous cell carcinoma	19 (27)
Large cell carcinoma	17 (24)
Unclassified NSCLC	5 (7)
Grading	
Undifferentiated	8 (11)
Poorly differentiated	23 (33)
Moderately differentiated	23 (33)
Well differentiated	1 (1)
Unknown	15 (21)
Metastases	
Lymph nodes	35 (50)
Lung	33 (47)
Bone	19 (27)
Adrenal glands	15 (21)
Liver	13 (19)
Pleura	9 (13)
Brain	4 (6)
Pretreatment	
Surgery (lung)	12 (17)
Radiotherapy	
Mediastinum/lung	2 (3)
Brain	2 (3)

PS, performance status; NSCLC, non-small cell lung cancer.

Table 2
Response to treatment

	No. of patients (%)
Intent-to-treat	70
Overall response	29 (41)
Complete response (CR)	1 (1)
Partial response (PR)	28 (40)
Stable disease (SD)	15 (21)
Progressive disease (PD)	26 (37)

Table 3
Haematological toxicity by cycle ($n=229$)

Toxicity	Word Health Organization grade			
	I	II	III	IV
	No. of cycles (%)	No. of cycles (%)	No. of cycles (%)	No. of cycles (%)
Leucopenia	35 (15)	28 (12)	28 (12)	13 (6)
Anaemia	73 (32)	19 (8)	2 (1)	1 (0.5)
Thrombocytopenia	17 (7)	18 (8)	5 (2)	2 (1)

Table 4
Haematological toxicity by patient ($n=70$)

Toxicity	World Health Organization grade			
	I	II	III	IV
	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)
Leucopenia	10 (14)	20 (29)	21 (30)	7 (10)
Anaemia	29 (41)	11 (16)	2 (3)	1 (1)
Thrombocytopenia	8 (11)	9 (13)	5 (7)	2 (3)

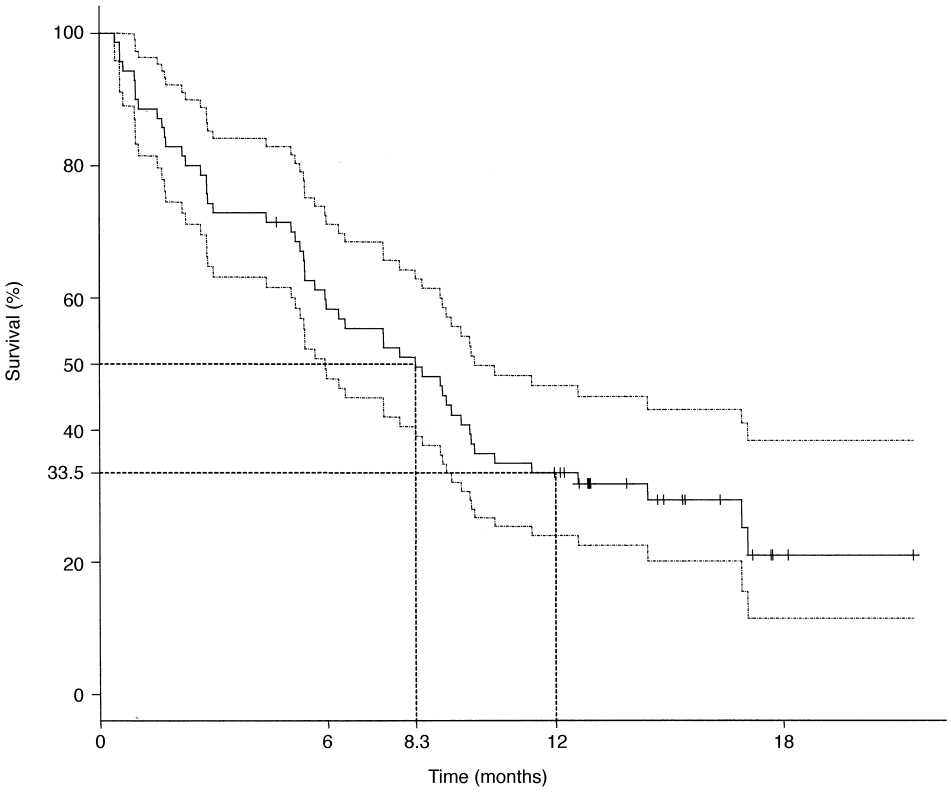

Fig. 1. Kaplan–Meier plot of overall survival ($n = 70$).

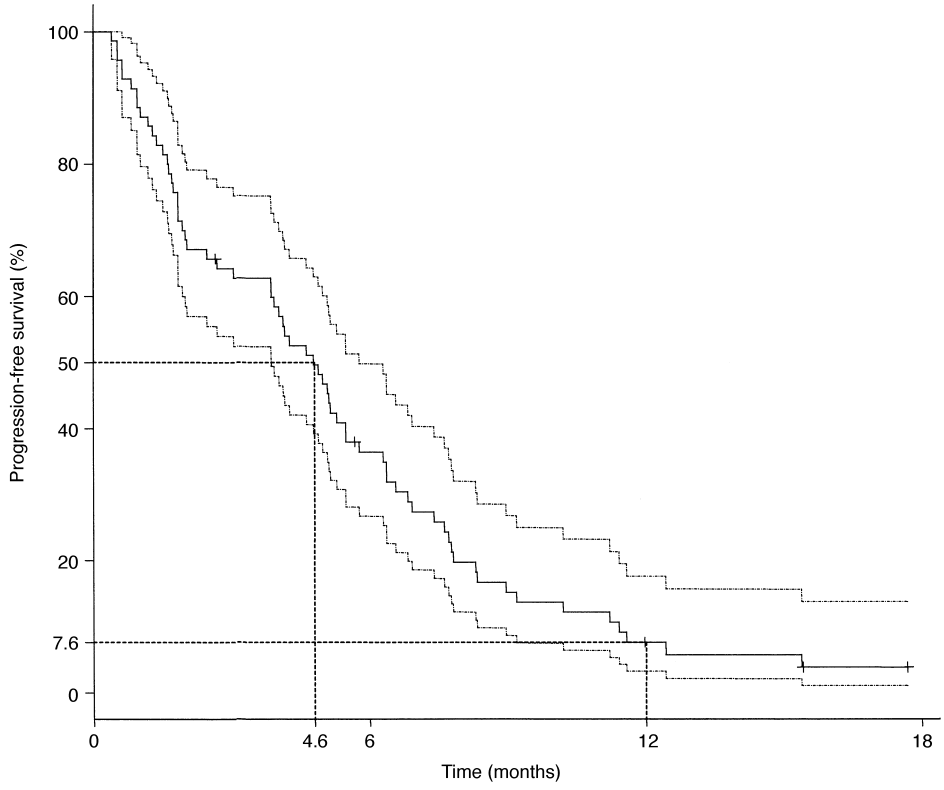

Fig. 2. Kaplan–Meier plot of progression-free survival (PFS) ($n = 70$).

Table 5
Non-haematological toxicity by patient ($n=70$)

Toxicity	World Health Organization grade			
	I	II	III	IV
	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)
Local phlebitis	12 (17)	14 (20)	5 (7)	0
Neurotoxicity	8 (11)	2 (3)	4 (6)	0
Mucositis	3 (4)	3 (4)	3 (4)	0
Constipation	5 (7)	0	2 (3)	1 (1)
Nausea/vomiting	19 (27)	8 (11)	7 (10)	0
Fatigue	22 (31)	7 (10)	1 (1)	0
ALT/AST	9 (13)	5 (7)	1 (1)	0
Cutaneous rash	9 (13)	3 (4)	1 (1)	0
Alopecia	24 (34)	5 (7)	1 (1)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

4. Discussion

New cytotoxic agents have broadened the therapeutic approach to metastatic NSCLC. The best benefit has been reported for substances such as vinorelbine, gemcitabine, docetaxel and paclitaxel. In phase II trials [10–13,22,23], single-agent therapy using these substances produced response rates of 15–30%, with median survival rates of 6–13 months and 1-year survival rates of up to 30%. When the new agents were combined with cisplatin or carboplatin in phase II trials [22–27], higher response rates of 25–60% were observed. These phase II trials also yielded higher median survival rates of 8–15 months and 1-year survival rates of 30–60%.

In this phase II trial, the combination of gemcitabine and vinorelbine demonstrated antitumour activity in metastatic NSCLC. We observed an overall intent-to-treat response rate of 41%, a median survival of 8.3 months (95% CI 6.0–9.9 months), and a 1-year survival of 33.5% (95% CI 24.0–46.8%). These results are comparable to those reported for platinum-containing combinations in phase II trials, as well as those of recently published phase II trials [18,20,28–35] of gemcitabine and vinorelbine. In these trials, the response rate for a combination chemotherapy containing gemcitabine and vinorelbine as first-line treatment varied from 19 to 72%, with an average of 31% among 590 patients. The average median survival has been reported as 9 months (range 7–13 months), the average median time to progression as 5.3 months (range 4–7 months), and the average 1-year survival rate as 37% (range 24–49%). There were slight differences in the schedules of these trials. Comparable our study, some authors also used a 4-week cycle, with administration of both drugs on days 1, 8 and 15. The doses of gemcitabine and vinorelbine varied between 800 and 1200 mg/m^2 and 20 and 30 mg/m^2, respectively [30–33]. However, in most of the trials, gemcitabine (1000–1200 mg/m^2) and vinorelbine (25–30 mg/m^2) were given on days 1 and 8 in a 3-week cycle [18,28,29,34,35]. Three-week, as well as 4-week, schedules are feasible and have equal activity, but myelosuppression did result in the inability to deliver full doses of therapy to most of the patients in a 4-week cycle. In particular, the day 15 was often delayed. Therefore a 3-week cycle with treatment on days 1 and 8 may result in more accurate drug delivery.

Gridelli and colleagues [35] compared in a phase II trial four dose-levels of gemcitabine and vinorelbine to identify the optimal dose given in a 3-week cycle. They observed that the regimen 1200 mg/m^2 gemcitabine and 30 mg/m^2 vinorelbine was unfeasible, because of WHO-grade IV neutropenia. The regimens 1000 mg/m^2 gemcitabine plus 25 mg/m^2 vinorelbine, 1200 mg/m^2 gemcitabine plus 25 mg/m^2 vinorelbine, and 1000 mg/m^2 gemcitabine plus 30 mg/m^2 vinorelbine were all well tolerated and showed equal antitumour activity, but the combination 1000 mg/m^2 gemcitabine plus 25 mg/m^2 vinorelbine had less frequent and less severe toxicity.

Regarding tolerability, gemcitabine and vinorelbine are active substances that in combination provide excellent symptom control in association with a favourable toxicity profile and this is also the case in elderly and unfit patients [33,34]. Furthermore, recent studies reported encouraging efficacy of gemcitabine plus vinorelbine as second-line chemotherapy in NSCLC [36,37].

A randomised phase II trial compared the combination of gemcitabine and vinorelbine with vinorelbine alone in elderly patients. The combination was more active resulted in a significantly better outcome compared with the single agent [38].

The sequence of drug administration chosen for this combination may have contributed to the comparatively high response rate observed in metastatic NSCLC in this study. Because gemcitabine is a pro-drug that is transformed intracellularly into its active metabolites, disphosphate and triphosphate, a high activity of deoxycytidine kinase is important for its metabolism [39]. However, the influence of the vinca-alkaloids on the transformation of gemcitabine into its active metabolites is unknown. Thus, we decided to administer gemcitabine first, followed 1 h later by vinorelbine.

As is characteristic of larger phase III trials [14,15,40–47], survival rates in these trials have not reached the levels attained in phase II trials; median survivals are generally from 8 to 10 months and 1-year survival rates are 30–43%. In two randomised trials, the combinations of gemcitabine plus cisplatin and vinorelbine plus cisplatin produced significantly higher response rates than those of cisplatin alone, as well as a significant survival benefit [40,41].

Survival rates obtained with new cytotoxic combinations, although improved, remain modest. Thus, NSCLC remains largely a palliative disease. Therefore,

we should continue giving high priority to the palliative aspect of chemotherapy to achieve symptomatic control and improve quality of life. To appropriately evaluate a new drug combination in terms of palliation, treatment should include a high proportion of patients with stage IV NSCLC (generally $\geqslant 80\%$), because locally advanced disease (stage IIIA/B) [48–51] is more chemosensitive compared with metastatic disease (stage IV), which is primarily palliative. It is important to note that in this study, only 16% of the patients had stage IIIB disease, while 84% had stage IV disease.

To investigate the role of cisplatin in combination with gemcitabine and vinorelbine in a palliative setting, we initiated a multicentre, randomised, phase III trial in September 1999 comparing 1000 mg/m^2 gemcitabine plus 25 mg/m^2 vinorelbine versus the same gemcitabine/vinorelbine regimen plus 75 mg/m^2 cisplatin in patients with stage IIIB (with malignant pleural effusion) and stage IV disease. To avoid treatment delays, gemcitabine and vinorelbine are being given on days 1 and 8 of a 3-week cycle (cisplatin is being given on day 2).

In conclusion, this phase II study of the combination of gemcitabine and vinorelbine has demonstrated activity in metastatic NSCLC, with response and survival rates similar to those of cisplatin-based regimens and a more favourable toxicity profile that is well tolerated in an outpatient setting. We believe that examining the combination of gemcitabine and vinorelbine is an important step toward finding a platinum-free standard regimen for patients with metastatic NSCLC, particularly when the goal is primarily palliative. Accordingly, a patient bearing an incurable disease should be offered a bearable treatment.

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