Phase I–II trial of low-dose gemcitabine in prolonged infusion and cisplatin for advanced non-small cell lung cancer

M. Zwitter, V. Kovac, U. Smrdel, I. Kocijancic, B. Segedin and M. Vrankar

After monotherapy with gemcitabine in low dose in long infusion, promising results in a variety of advanced chemoresistant tumors have been reported. In a previous phase I trial on heavily pre-treated patients, maximum tolerated dose (MTD) of gemcitabine in a 6 h infusion was 250 mg/m^2. The objective of our phase I–II trial was to test the combination of gemcitabine in a 6-h infusion and cisplatin in the treatment of advanced non-small cell lung cancer (NSCLC). Eligible patients were chemonaive, had locally advanced or metastatic NSCLC, Eastern Oncology Cooperative Oncology Group performance status 0–2 and normal organ function. Treatment consisted of gemcitabine in a 6-h infusion on days 1 and 8, and cisplatin at 75 mg/m^2 on day 2 of a 3-week cycle. During phase I of the trial, the dose of gemcitabine was escalated from 130 to 170, 210 and 250 mg/m^2. After establishing dose-limiting toxicity (DLT) and MTD of the combination, the trial continued as phase II. Altogether, 61 patients were enrolled, of whom 54 had stage IV disease. In phase I of the trial, groups of six, seven, eight and eight patients were treated at the four dose levels of gemcitabine. In phase II, the remaining 32 patients all received gemcitabine at 250 mg/m^2. Serious toxicity included a patient with grade 5 ventricular arrhythmia and another with grade 4 cerebrovascular ischemia; four patients had grade 3 anemia. Reversible thrombocytosis with platelets over 500 was recorded in 32 patients; 42 patients had grade 2 alopecia. In general, tolerance to this treatment was good. One patient had complete response and 27 had partial responses, for a 28 of 61 (46%) response rate. Median progression-free survival, median survival and 1-year survival were 6 months, 9.5 months and 40%, respectively. We conclude that this treatment has an acceptable, yet distinct, toxicity profile; routine thromboprophylaxis is recommended. In our population of chemonaive patients, no DLT has been encountered. Due to the remarkable response rate, further research is warranted. *Anti-Cancer Drugs* 16:1129–1134 © 2005 Lippincott Williams & Wilkins.

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Institute of Oncology, Ljubljana, Slovenia.

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Correspondence to M. Zwitter, Institute of Oncology, Zaloska 2, 1000 Ljubljana, Slovenia.
Tel: +386 31 687546; fax: + 386 1 5879400;
e-mail: mzwitter@onko-i.si

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Introduction

According to the dose rate and to the corresponding maximum tolerated dose (MTD), gemcitabine has been applied in three distinct schedules. For the usual 30-min infusion (dose rate 40 mg/m^2/min) and for the moderately prolonged 100-min infusion (dose rate 10 mg/m^2/min), MTD is 1500 mg/m^2 or even higher [1,2]. With lower dose rates, MTD falls significantly. With infusions lasting for 3, 6 or 24 h, MTD falls to 450, 250 and 180 mg/m^2, respectively [3–6]. The explanation for this phenomenon lies in the saturation of deoxycytidine kinase which occurs after short infusion at conventional doses. This enzyme is needed for conversion of gemcitabine into its active form gemcitabine triphosphate. While short infusion leaves most of the drug unmetabolized, prolonged infusion leads to a higher intracellular concentration of the active metabolite [4,7].

For the purpose of our discussion, the term 'prolonged infusion' will be limited to infusions longer than 3 h and with a dose rate of below 2.5 mg/m^2/min. With single-agent gemcitabine in prolonged infusion, good preliminary results were reported for patients with heavily pre-treated breast cancer, Hodgkin's disease or soft-tissue sarcomas and for chemonaive patients with advanced pancreatic cancer [8–11].

While several trials of gemcitabine at the intermediate dose rate of 10 mg/m^2/min in combination with other drugs have been reported [12–17], there have been no attempts to combine gemcitabine at the very low dose rate with other cytotoxic drugs.

Here, we here report a phase I–II trial designed to assess the toxicity and efficacy of low-dose gemcitabine in prolonged infusion when combined with standard cisplatin for patients with advanced non-small cell lung cancer (NSCLC).

Patients and methods

Chemonaive patients were eligible for this trial if they had histologic or cytologic diagnosis of NSCLC, Eastern

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Cooperative Oncology Group (ECOG) performance status (PS) 0–2, stage IIIB with cytologically positive pleural effusion or stage IV, measurable and previously unirradiated lesion, no clinical evidence of brain metastases, and adequate hematopoietic, liver and kidney function. All patients were fully informed and gave written consent to participate in the trial.

Within 2 weeks prior to treatment, measurable lesions were defined. In the absence of neurologic symptoms, brain computed tomography was not required.

The general treatment schedule was identical for all patients: gemcitabine in a 6 h infusion on days 1 and 8, and cisplatin at 75 mg/m^2 on day 2 of a 3-weekly cycle. After 4 cycles, those not in progression and without serious toxicity continued with an additional 2 cycles of monotherapy with gemcitabine in prolonged infusion.

In phase I of the trial, the dose of gemcitabine was escalated from the initial 130 to 170, 210 and 250 mg/m^2, with the aim of establishing the MTD for the combination of gemcitabine in prolonged infusion and cisplatin. In case of an acceptable level of toxicity and at least a 15% response rate, the trial would continue as a phase II.

National Cancer Institute Common Toxicity Criteria (CTC) version 2.0 were used for grading the toxicity. Response was assessed during the third and fifth cycles using the RECIST criteria [18].

The trial was approved by the Protocol Review Board of the Institute of Oncology and by the National Committee for Medical Ethics.

Survival times were calculated from the first day of chemotherapy; 1 April 2005 was the close-out date for data collection. The results were analyzed using a PC and the SPSS statistical package (release 10.0; SPSS, Chicago, Illinois, USA). Univariate analysis of progression-free survival (PFS) and overall survival (OS) was done with the Kaplan–Meier product-limit method [19].

Results

Between January and December 2003, 61 chemonaive patients with advanced NSCLC entered the trial. The demographic data are presented in Table 1.

Table 1 Patient characteristics

Patients (*n*)	61
Median age [years (range)]	58 (31–76)
Gender [*n* (%)]	
male	43 (70.5)
female	18 (29.5)
ECOG PS [*n* (%)]	
0	16 (26.2)
1	29 (47.6)
2	16 (26.2)
Stage [*n* (%)][a]	
IIIB	7 (11.4)
IV	54 (88.6)
Histology [*n* (%)]	
squamous cell carcinoma	15 (24.6)
adenocarcinoma	36 (59.0)
large cell and NSCLC, unspecified	10 (16.4)
Sites of active disease[b] [*n* (%)]	
lung, primary and mediastinum[c]	44 (72.1)
pleura	12 (19.7)
lung, distant	33 (54.1)
bone	15 (24.6)
liver	11 (18.0)
suprarenals	8 (13.1)
distant lymph nodes and soft tissues	7 (11.4)
Dose of gemcitabine (mg/m^2/6 h) [*n* (%)]	
130	6 (9.8)
170	7 (11.4)
210	8 (13.1)
250	40[d] (65.6)

[a]At registration for this trial.
[b]More than one site of disease per patient may apply.
[c]Some patients had the primary controlled by previous surgery and/or radiotherapy.
[d]Eight patients within phase I and 32 within phase II of the trial.

Treatment: phase I and phase II of the trial

The trial started as phase I, with escalation of the dose of gemcitabine on days 1 and 8: 130 ($n = 6$), 170 ($n = 7$), 210 ($n = 8$) and 250 mg/m^2 ($n = 8$). On day 2, all patients received cisplatin at 75 mg/m^2.

In the phase I part of the trial, no serious or dose-limiting toxicity (DLT) was seen. A detailed report on toxicity will be presented for all 61 patients included in both phases of the trial.

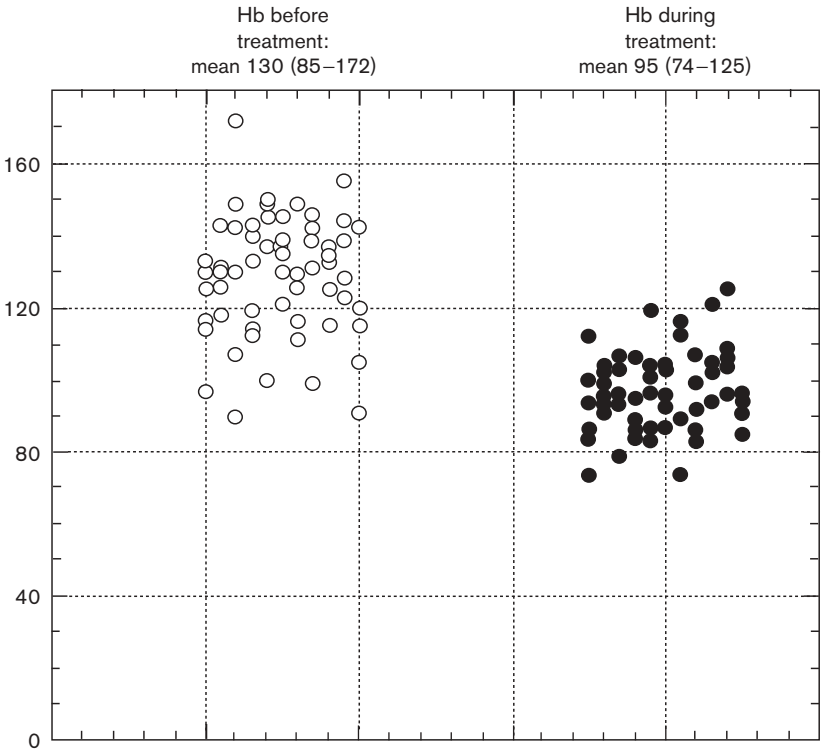
Among the first 29 patients, one complete and 13 partial remissions were seen. On the basis of acceptable toxicity and promising activity, the trial continued into phase II and recruited an additional 32 patients for gemcitabine at 250 mg/m^2.

After the initial 4 cycles of gemcitabine/cisplatin, 38 patients received an additional 1 or 2 cycles of monotherapy with gemcitabine in prolonged infusion. On average, 4.6 cycles of chemotherapy were applied.

Toxicity

Five patients experienced serious toxicity, due to which treatment had to be interrupted. Two days after the first application of gemcitabine and cisplatin, a 66-year-old male patient with diffuse lung metastases developed ventricular arrhythmia and died in cardiorespiratory failure 8 days later. Also after the first cycle, a 64-year-old woman with a history of hypertension developed grade 4 cerebrovascular ischemia; 8 months later, she died of progressive disease. Two patients had grade 2 vascular toxicity – superficial phlebitis on the legs leading to ulceration and reversible ischemia of the great toe on a foot. After discontinuation of the treatment, the condition in these two patients resolved.

Fig. 1



Hemoglobin level (g/l) before treatment and at nadir during chemotherapy.

Nausea and vomiting (grade 3 in 12 patients) were common, but manageable. Most experienced alopecia (grade 2 in 42 patients). Anemia was common: grade 2 in 34 patients and grade 3 in four patients (Fig. 1). Leukopenia and neutropenia (grade 3 in 7 patients and grade 4 in one patient) were rare; no patient had febrile neutropenia. While thrombocytopenia (grade 3 in one patient) was exceptional, most patients had reversible thrombocytosis with platelets over 500 in 32 patients and over 1000 in three patients (Fig. 2).

Four patients had grade 2 renal toxicity; none had hepatotoxicity of grade 2 or greater. Detailed data on toxicity and on its relation to the dose of gemcitabine are shown in Table 2.

Tumor response, treatment after progression and survival

One complete response and 27 partial responses gave an overall response rate of 28 of 61 (46%). An additional 20 patients had stable disease. The dose of gemcitabine had no clear influence upon response: among responders were 10 of 21 patients treated with gemcitabine at 130–210 mg/m^2 and 18 of 40 of those treated with 250 mg/m^2. Data on responses, PFS and OS for subgroups of patients are presented in Table 3.

The median time to progression was 6 months, with lung (33 patients) as the most common site of progression. Second-line chemotherapy was given to four patients; the remaining were offered palliative radiotherapy and supportive treatment.

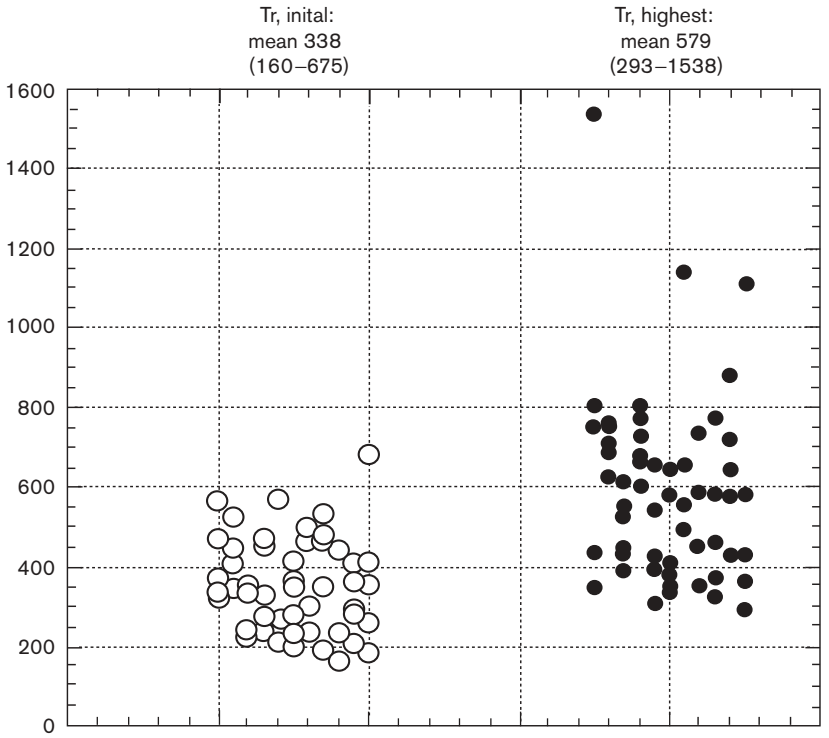
All patients were regularly followed every 2 months. No patient was lost to follow-up.

After an observation period of 16–27 months, 15 patients are alive. Median survival is 9.5 months. One-year survival is 40% (Fig. 3).

Discussion

Synergistic activity of gemcitabine and cisplatin has been shown *in vitro* and in many clinical trials. While the combination of cisplatin and gemcitabine at a high dose rate (above 30 mg/m^2/min, total dose 800–1250 mg/m^2) is widely accepted, our trial is the first report on a phase I–II trial of gemcitabine at below 1 mg/m^2/min in combination with cisplatin. The population of chemonaive patients and escalation of the dose of gemcitabine allowed us to address the question of MTD and to explore the activity of this approach in advanced NSCLC.

Fig. 2



Platelets ($\times 10^9$/l) before treatment and at the highest level during chemotherapy.

Table 2 Toxicity (CTC grade)

	Dose of gemcitabine (mg/m^2/6 h)					
	130–210 (21 patients)			250 (40 patients)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Anemia	16	1		18	3	
Neutropenia	1			14	7	1
Thrombocytopenia					1	
Thrombocytosis[a]	13			19	2	1
Thromboembolic and cardiovascular	2					2[b]
Nephrotoxicity	2			2		
Nausea and vomiting	6	3		8	9	
Alopecia	11			31		

[a]Not specified in NCI CTC, version 2.0. In this table, grade 2: 501–1000 $\times 10^9$/l; grade 3: 1001–1500 $\times 10^9$/l; grade 4: >1501 $\times 10^9$/l.
[b]One patient with grade 4 and one with grade 5 cardiovascular toxicity.

In our single-institution trial, 61 patients were recruited within only 11 months. Since virtually all eligible patients seen during 2003 entered the trial, the experience is relevant for a broader population of patients with advanced NSCLC. Also important is the fact that only seven (11%) of our patients had stage IIIB 'wet' disease. The high proportion of patients with metastatic disease in our trial should be considered when comparing our experience to other trials of advanced NSCLC.

Patients included in previous trials of monotherapy with gemcitabine in a 6-h infusion were all heavily pre-treated and resistant to conventional therapies. On such a population, 250 mg/m^2/6 h was reported as the MTD for single-agent gemcitabine; hepatotoxicity and myelotoxicity were the DLTs [4,6]. We reached this level of gemcitabine in combination with cisplatin and did not encounter any DLT. It may well be that chemonaive patients can tolerate even higher doses of gemcitabine in prolonged infusion. Nevertheless, we found no dose–response relationship in the range between 130 and 250 mg/m^2/6 h, and therefore decided not to escalate the dose of gemcitabine above this level.

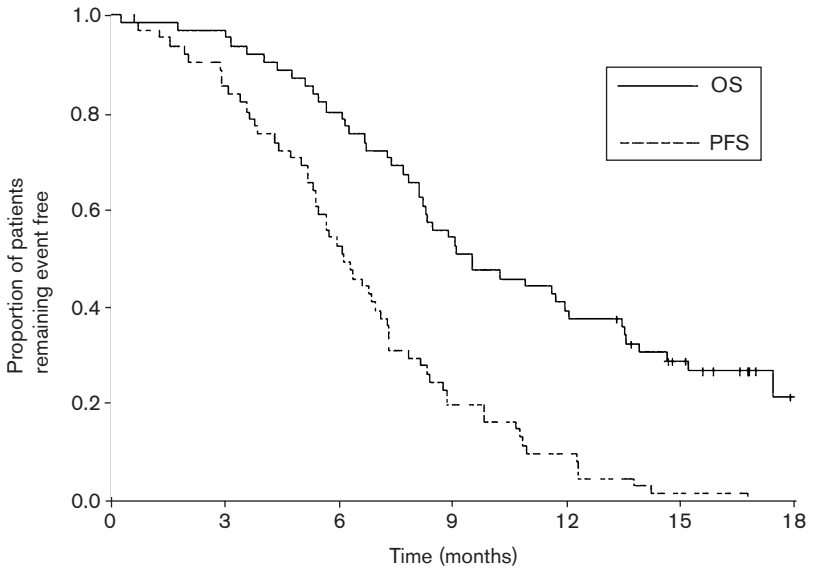
When compared with the usual experience with a 5 times higher dose infused over 30 min, gemcitabine in

Table 3 Data on responses, PFS and median survival for subgroups of patients

	No. of patients	Objective responses (CR + PR)	Median PFS (months)	Median survival (months)
Gender				
female	18	11	6.1	12.0
male	43	17	6.2	9.5
Age (years)				
≤ 60	34	18	6.2	12.0
>60	27	10	5.8	9.1
ECOG PS				
0	16	9	7.2	14.6
1	29	14	5.8	9.0
2	16	5	5.7	8.3
Stage				
III B[a]	7	0	6.2	13.9
IV	54	28	6.0	9.1
Histology				
squamous	15	7	6.8	10.2
adenocarcinoma	36	16	6.0	9.0
large cell and unspecified	10	5	6.0	11.7
Gemcitabine (mg/m^2/6 h)				
130–210	21	10	5.8	8.1
250	40	18	6.3	11.9

[a]All with malignant pleural effusion.

Fig. 3



PFS and OS.

prolonged infusion appears as a different drug with a clearly distinct toxicity profile. Only a randomized trial could offer a reliable comparison of toxicity of gemcitabine in short or long infusion, both in combination with cisplatin. Nevertheless, we can say that anemia, thrombocytosis and alopecia are more prominent with the prolonged infusion; however, neutropenia and thrombocytopenia are rare.

The four cases with cardiovascular or thromboembolic adverse events deserve proper attention. In each individual case, the contribution of the treatment, of the treatment-induced thrombocytosis, of metastatic cancer and of concomitant diseases remains unclear. With our limited experience, two recommendations can be made. First, patients with a history of thromboembolic or cardiovascular morbidity should be treated with extreme caution or offered alternative schedules of chemotherapy. Second, routine thromboprophylaxis should be considered. In our own experience, not a single thromboembolic event was recorded among the additional 55 patients treated since December 2003 when we opened a new trial and introduced low-molecular-weight heparin as part of routine supportive treatment.

The number of patients included in our trial is limited and does not permit a precise assessment of this treatment approach. When comparing our experience to other trials for advanced NSCLC, we would like to point to the unusually high percentage of stage IV disease in our trial and the virtual absence of second-line chemotherapy – a treatment which might prolong survival after relapse. With this in mind, the 46% response rate, 9.5 months as mean survival and 40% 1-year survival may be regarded as promising.

At present, low-dose gemcitabine in prolonged infusion in combination with cisplatin should be offered only within a carefully planned clinical trial. The experience is far too scarce to recommend this treatment as routine and, especially, not with the aim of reducing the costs. While the standard brief infusion of gemcitabine is easily given on an outpatient basis, prolonged infusion involves additional costs for hospitalization and transportation. In the economic analysis, lower costs for the drug should be balanced against greater other costs.

In conclusion, treatment with low-dose gemcitabine in prolonged infusion in combination with cisplatin is feasible. The toxicity clearly differs from the common experience with cisplatin and gemcitabine in the standard dose and short infusion. While neutropenia and thrombopenia were rare, anemia, thrombocytosis and alopecia were common. Four cases of cardiovascular and thromboembolic toxicity may be partly attributable to advanced cancer and to comorbidity; nevertheless, routine thromboprophylaxis is recommended.

The most challenging message of our trial is the remarkable response rate. As the next step, comparison to the standard brief infusion of gemcitabine is warranted.

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