Two schedules of chemotherapy for patients with non-small cell lung cancer in poor performance status: a phase II randomized trial

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We present experience from a phase II randomized clinical trial, comparing standard gemcitabine as monotherapy with low-dose gemcitabine in long infusion in a doublet with cisplatin at reduced dose for patients with non-small cell lung cancer (NSCLC) and who are unfit for standard platin-based chemotherapy. Eligible patients had microscopically confirmed NSCLC in stage IIIB (wet) or IV, were chemo-naive, and were in poor performance status or presented with significant comorbidity. Standard treatment with gemcitabine, 1250 mg/m^2 in 20–30 min on days 1 and 8 as monotherapy (arm A) was compared with low-dose gemcitabine in long infusion (200 mg/m^2 in 6 h on day 1) and cisplatin at 60 mg/m^2 on day 2 (arm B). Both treatment schedules were repeated every 3 weeks until disease progression, unacceptable toxicity, or to a maximum of six cycles. A total of 112 patients (83 male, 29 female, median age 66 years) were randomized between arm A (57 patients) and B (55 patients). The two groups were balanced for prognostic factors. Fifty-three patients in arm A and 52 in arm B received at least one application of chemotherapy and were evaluable for toxicity and response. The median number of cycles was four and five for arms A and B, respectively. Except for grade 3 anemia (one patient in arm A and two in arm B), no other major toxicity was seen. Regarding response to treatment, arm B was superior: 1 complete response and 13 partial remissions (response rate 26.9%) as compared with five partial remissions (response rate 9.4%) in arm A ($P<0.01$). The median time to progression was 3.8 and 5.6 months, and the median survival was 4.3 and 6.8 months for arms A and B, respectively ($P<0.05$). Treatment with low-dose gemcitabine in long infusion and cisplatin at reduced dose has very low toxicity, is effective, was found to be superior to monotherapy with gemcitabine in standard doses, and is suitable for patients with NSCLC who cannot tolerate a standard platin-based doublet. *Anti-Cancer Drugs* 21:662–668 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

A substantial proportion of patients with advanced non-small cell lung cancer (NSCLC) are not fit enough to receive standard full-dose chemotherapy with a platin-based doublet. Poor performance status, reduced mobility because of bone or brain metastases, significant comorbidity, impaired renal, cardiac, hematologic or hepatic function, or very advanced age are among the reasons for the reluctance to use standard chemotherapy. In the ELVIS trial specifically designed for elderly patients with advanced NSCLC, a single-agent therapy with vinorelbine was compared with the best supportive care and was found to be superior in terms of quality of life and survival [1]. Several other phase II trials reported acceptable toxicity, modest activity, and improvement in symptom control, using single-agent therapies with gemcitabine, vinorelbine, paclitaxel or pemetrexed [2–7]; gefitinib or erlotinib may be preferred for patients with proven or suspected activating mutations of epidermal growth factor receptor [8]. Single-agent therapy is therefore the recommended approach in the European and American guidelines [9,10]. Yet, most improvements are of short duration and median survival rarely exceeds 6 months. To improve the prospects for such a fragile patient population, new effective treatments of low toxicity should be explored [11].

Our earlier research indicated that low-dose gemcitabine in long infusion in combination with cisplatin is a treatment of low toxicity and promising activity against NSCLC [12]. This favorable experience was confirmed in a subsequent randomized trial in which patients in good performance status were treated either with standard gemcitabine (1250 mg/m^2/30 min), or with low-dose gemcitabine in long infusion (250 mg/m^2/6 h); both arms also received cisplatin at 75 mg/m^2. Patients treated with low-dose gemcitabine in long infusion had more objective responses and reported better quality of life. Although progression-free survival and overall survival were identical in both treatment arms, there was a trend towards longer progression-free survival and overall survival for patients with squamous carcinoma [13].

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We present experience from another randomized phase II trial designed to suit patients in poor performance status. As these patients may not tolerate the standard cisplatin–gemcitabine doublet, our schedule included a lower dose of gemcitabine (200 mg/m^2 in 6 h infusion), a lower dose of cisplatin (60 mg/m^2), and we omitted gemcitabine on day 8 of the treatment cycle. This mild doublet was compared with monotherapy with gemcitabine as the standard arm.

The primary objective of our trial was overall survival; secondary objectives were progression-free survival, response rate, treatment toxicity, and quality of life.

Patients and methods

Eligibility criteria

Patients eligible for the trial had cytologically or histologically confirmed NSCLC in stage IIIB (wet) or IV and were chemo-naive. Measurable disease was not essential. In addition, the patients had to meet at least one of the exclusion criteria for a clinical trial with the standard platin-based doublet:

(1) performance status 60–70% (Karnovsky) or Eastern Cooperative Oncology Group 2–3;
(2) hemoglobin 80–100 g/l;
(3) renal impairment with creatinine 1.1–1.5 × UNL;
(4) liver impairment with bilirubin 1.1–1.5 × UNL;
(5) symptomatic brain metastases after radiotherapy and/or surgery;
(6) other primary malignancy, not in complete remission during the past 3 years.

Pretreatment diagnostics were limited to the essential examinations: endoscopy with tumor verification, chest radiograph, CT scan of the thorax and upper abdomen, and blood and biochemistry tests.

All the patients were fully informed about the trial and signed the consent form.

Registration and randomization

Patients were registered for the trial by e-mail to the data manager of the unit of clinical research. Randomization between the arms A (gemcitabine as monotherapy) and B (low-dose gemcitabine in long infusion and cisplatin at reduced dose), 1 : 1, was done using a computer-generated sequence of random numbers. After registration, all the patients were considered as participating in the trial, regardless of the treatment which they actually received.

Treatment

Arm A – Gemcitabine monotherapy (standard treatment)

Days 1 and 8: Gemcitabine, 1250 mg/m^2 in 20–30 min infusion

The cycle was repeated on day 22.

Arm B – Low-dose gemcitabine in prolonged infusion and cisplatin at reduced dose

Day 1: Gemcitabine, 200 mg/m^2 over 6 h

Day 2: Cisplatin, 60 mg/m^2 with appropriate hydration and antiemetics

Cycle duration as above.

The treatment was continued for a maximum of six cycles or until progression, unacceptable toxicity, or deterioration of the patient's performance status.

Virtually all the treatment was delivered in a day hospital.

Treatment modification and supportive treatment

The dose of gemcitabine was reduced to 75% in the case of moderate neutropenia (range 1.5–2.0 × 10^9/l) or thrombocytopenia (range 75–140 × 10^9/l) and omitted if the neutrophils and/or platelets fell below this range. Cisplatin was omitted for creatinine above 1.5 × UNL or in case of grade III nausea or vomiting during the earlier cycle.

Evaluation for response, quality of life, and toxicity

During cycles 3 and 5, a chest radiograph and/or CT scan were repeated to assess tumor response, using the same method as during initial imaging.

Eastern Cooperative Oncology Group performance status was recorded monthly. During cycles 3 and 5, we used our own simplified scale for assessment of quality of life:

How do you feel in comparison with your feeling before the treatment?

(1) much worse
(2) worse
(3) about the same
(4) better
(5) much better.

Side effects of the treatment were assessed according to the NCI Common Toxicity Criteria, version 2.0.

Follow-up, evaluation for progression, and second-line treatment

After the treatment, patients in the good performance status were invited to follow-up visits every second month. In addition to clinical examination and blood tests, chest radiograph or other appropriate imaging was repeated to assess the site(s) of active disease. Patients in the poor performance status continued their symptomatic treatment with their general practitioner or in a regional hospital and were regularly contacted by telephone.

In the case of progression, every effort was made towards effective palliation of the leading symptoms. Additional systemic treatment was always discussed with the patient and at the tumor board. Treatment was never prolonged if it led to an unbearable quality of life.

Ethical issues and statistical considerations

The investigators strictly followed recommendations of the Helsinki declaration (1964, with later amendments) and of the European Council Convention on Protection of Human

Rights in Bio-Medicine (Oviedo 1997). The protocol was approved by the Institutional Review Board (Institute of Oncology, Ljubljana) and by the National Committee for Medical Ethics, Ministry of Health, Republic of Slovenia.

The data were described as the absolute numbers with corresponding relative frequencies. The χ^2 test was used to examine the difference in the prognostic factors between the arms. Progression-free survival has been defined as the time from the date of randomization to the date of disease progression or death (two events, whichever occurred first). Median progression-free and overall survival was estimated by the Kaplan–Meier survival curves; groups were compared using the log-rank test. The effects of the treatment modality on survival were analyzed by the Cox model, allowing us to control the results for age, sex, histological type, and weight loss. A P value of less than 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software package (version 16.0).

The trial size was defined according to the expected accrual of patients in our institution within 3 years. Although the limited size and low power of such a trial rarely leads to a statistically clear comparison, it may offer a valuable orientation for further clinical research [14].

Results

Patient population

Between April 2005 and October 2008, virtually all eligible patients seen at the Institute of Oncology in Ljubljana were invited to participate in the trial, and more than 80% consented to join the trial. In total, 112 patients were recruited in the trial. Data on demographics and on prognostic factors are presented in Table 1.

Adenocarcinoma (52 patients) and squamous carcinoma (42 patients) were the most common tumour types. Over 95% of the patients had stage IV disease with distant lung metastases as the most common site of metastatic disease, followed by brain, liver and bone metastases (Table 3). Two or more sites of metastatic disease were documented in 26 patients (45.6%) and 29 patients (52.7%) for the treatment arms A and B, respectively (Table 2).

Treatment

During the interval between the patient's registration for the trial and the actual start of chemotherapy, the general condition of nine patients (four randomized into arm A and five into arm B) deteriorated to such a degree that they received supportive treatment only. These patients are not included in the statistics of the response to treatment, toxicity, quality of life, and time to progression, but remain in the trial for survival as the primary endpoint.

In both treatment arms, 39 patients received at least three cycles of chemotherapy. All six cycles of chemotherapy were given to 19 and 23 patients in arms A and B, respectively (Table 3).

Table 1 Demographics, smoking and prognostic factors

	ARM A Gemcitabine monotherapy 57 patients	ARM B Low-dose long infusion gem – cis 55 patients
Age (years)		
Median	66	65
Range	40–81	49–80
Sex		
Male	46	37
Female	11	18
Smoking		
Never smoker	4	8
Former, quit at >2 years	20	12
Smoked until current disease	23	23
Current smoker	10	12
Previous other cancer	3	1
Performance status		
ECOG 2	15	12
ECOG 3	42	43
Weight loss		
<10%	40	41
≥ 10%	17	14
Hematology & biochemistry		
Hb <100 g/l	3	4
Creatinine 96–145	9	8
Bilirubin 20–30 μmol/l	2	0

ECOG, Eastern Cooperative Oncology Group.

Table 2 Histology, stage and sites of metastatic diseaase

	ARM A Gemcitabine monotherapy 57 patients	ARM B Low-dose long infusion gem – cis 55 patients
Histology		
Squamous	26	16
Adeno	22	30
Large cell	3	3
Poorly differentiated & NSCLC, undefined	6	6
Stage		
IIIB	2	3
IV	55	52
Sites of metastatic disease		
Pleura, pericardium	7	7
Lung – distant metastases	30	25
Liver	14	10
Suprarenals	8	10
Bone	13	10
Distant lymph nodes, soft tissues	3	8
Brain, after RT ± surgery	15	19

Toxicity

In general, both treatments were tolerated very well. Three patients (one in arm A and two in arm B) had grade 3 anemia. Grade 2 toxicity included anemia, neutropenia, and nephrotoxicity and was equally distributed between both treatment arms (Table 4). No patient experienced grade 4 or greater toxicity.

Among patients who received at least three cycles of chemotherapy, grade 2 alopecia was seen in three of the 39 (8%) patients in arm A and in 25 of the 39 (64%) patients in arm B ($P < 0.01$).

Response to treatment and quality of life

Fifty-two patients in arm A and 50 in arm B received at least one application of chemotherapy and are evaluable

Table 3 Parameters of chemotherapy

	ARM A Gemcitabine monotherapy 57 patients	ARM B Low-dose long infusion gem – cis 55 patients
Cycle	No. of patients entering the cycle	
2	45	43
3	39	39
4	29	37
5	26	32
6	19	23

Table 4 Toxicity

	Grade	ARM A Gemcitabine monotherapy 57 patients	ARM B Low-dose long infusion gem – cis 55 patients
Anemia	2	7	11
	3	1	2
Neutropenia	2	5	3
Nephrotoxicity	2	1	2

for response. In arm A, five patients had a partial response and the remaining 28 had minimal response or stable disease, for an overall disease control rate of 33/52 (63.5%). In arm B, one patient had complete response, 13 patients had partial response, and 26 experienced minimal response or stable disease, leading to a disease control rate of 40/50 (80%). The difference in favour of group B is significant ($P < 0.01$).

Forty-seven patients in arm A and 45 in arm B were evaluable for self-assessment of quality of life. At cycle 3, 33 (70.2%) of patients in arm A reported equal or better general well-being, as compared with their pretreatment status. The corresponding figure for arm B is 39 (86.7%; $P < 0.05$) (Table 5).

Time to progression, second-line treatment and survival

Median time to progression for arms A and B was 3.8 and 5.6 months, respectively ($P < 0.02$; Fig. 1).

Three patients in arm A and six patients in arm B received second-line systemic treatment with chemotherapy (one patient from arm A) or erlotinib (all other patients).

No patient was lost to follow-up. The median overall survival was 4.3 and 6.8 months, and 1-year survival was 8.8 and 25.4% for arms A and B, respectively ($P < 0.05$; Fig. 2). In a multivariate analysis using the Cox regression model, treatment group (B better than A, $P = 0.003$), initial hemoglobin level ($P = 0.02$) and less than 10% weight loss ($P = 0.04$) were independent predictors for longer survival.

Discussion

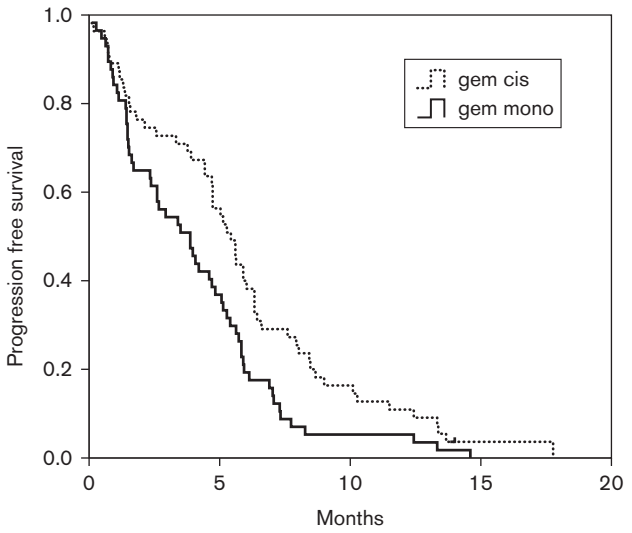
Defining the optimal systemic treatment for patients with NSCLC in poor performance status is one of the major challenges for thoracic oncology. Thirty to 40% of patients with advanced NSCLC are not fit enough to receive standard platin-based chemotherapy [15]. Yet, the proportion of these patients among all patients with NSCLC who were recruited into the randomized clinical trials has decreased from 32% in the 1980s to 12% in the last decade [16]. It is unlikely that the average performance status of the recent population of patients with advanced NSCLC has improved. Rather, sponsors are now more selective in defining the eligibility criteria and tend to exclude patients with comorbidity and/or poor performance status. In addition, clinical investigators are reluctant to recruit patients for whom they may

Table 5 Response to treatment, performance status and quality of life

	ARM A Gemcitabine monotherapy 57 patients	ARM B Low-dose long infusion gem – cis 55 patients
Response to treatment		
CR	0	1
PR	5	13
MR + SD	28	26
Progression	20	10
Non-evaluable	4	5
QOL: Patient's self-assessment at cycle 3		
5	0	0
4	10	18
3	23	21
2	12	4
1	2	2
Non-evaluable	10	10

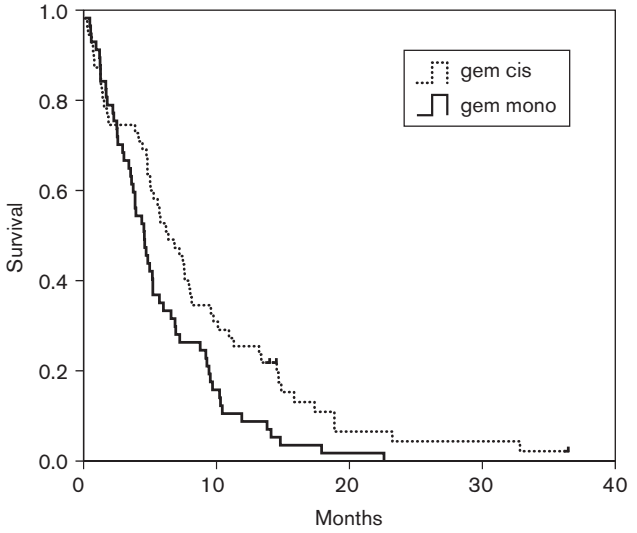
CR, complete response; MR, minimal response; PR, partial response; QOL, quality of life; SD, stable disease.

Fig. 1



Progression-free survival: significantly longer with low-dose gemcitabine in long infusion and cisplatin versus monotherapy with gemcitabine ($P < 0.02$).

Fig. 2



Overall survival: significant advantage of the doublet versus monotherapy with gemcitabine ($P<0.05$).

foresee difficulties in compliance with the strict RECIST rules, and a higher probability of toxicity leading to time-consuming reporting of serious adverse events.

Treatment for patients in poor performance status and/or with significant comorbidity should be devoid of major toxicity, as shown by the sentence: *Treatment should not be worse than the disease*. In addition, trials focusing on this frail population should avoid excessive diagnostics. Instead of the RECIST rules that demand measurement and confirmation of response at all sites of the disease, it is preferable to monitor response on a single site with a simple examination such as a chest radiograph. Another difference between standard trials and those specifically designed for patients in poor performance status is the end point chosen to monitor evolution of the disease. In trials for patients in good performance status, the preferred end point is time to progression, which is not influenced by the second-line treatment. However, second-line treatment is rarely applied to patients in poor performance status in whom we also wish to avoid frequent visits during the follow-up period. For these reasons, overall survival may be the most suitable primary end point for this frail population of patients.

Most trials for patients in poor performance are rather small, and ours with 112 patients is not an exception. In comparison, 14 clinical trials designed specifically for patients in poor performance status, and quoted among the references, recruited a median of 87 (range 16–400) patients. We wish to emphasize, however, that the size of a trial is not the only criterion for its validity. The crucial elements are honesty in registration, randomization, and reporting. Small phase II randomized clinical trials may contribute valuable new knowledge for subsequent incorporation into larger meta-analyses [14].

This trial developed as a side-product of a larger trial for patients in good performance status treated either with a standard gemcitabine–cisplatin schedule or with a doublet of low-dose gemcitabine in long infusion and cisplatin [13]. Soon after the activation of this trial, we realized that a substantial proportion of our patients were not eligible, mostly because of co-morbidity or poor performance status. These frail patients were then invited to a new trial comparing gemcitabine as monotherapy with a mild doublet of gemcitabine in long infusion and low-dose cisplatin.

An obvious obstacle to the interpretation of the results of our trial is its design. Patients in both the treatment arms received treatment on 2 days within a 3-week cycle: on days 1 and 8 in the gem-mono arm, or on days 1 and 2 in the mild doublet arm. In spite of this similarity, the design includes two variables: a different schedule for application of gemcitabine and addition of low-dose cisplatin to one of the treatment arms. We believe that low-dose cisplatin definitively contributed to the superiority of the doublet. The open question is the role of low-dose gemcitabine in long infusion. In spite of the lack of commercial interest, promising experience with this treatment for NSCLC, sarcomas, mesothelioma, heavily pretreated Hodgkin's disease, breast, pancreatic and bladder cancer has been reported from areas and countries as diverse as Europe, Egypt, India, and China [12,13,17–23]. The key difference between the standard brief application of gemcitabine and prolonged infusion is the proportion of the drug converted into the active triphosphate form. A high dose of the drug applied over a short period of time leads to saturation of the enzyme deoxycytidine kinase responsible for this conversion [24,25]. In contrast, long infusion leads to a much higher conversion rate, different pharmacokinetics, significantly lower maximal tolerated dose, different toxicity profile (including e.g. alopecia), and an apparently different spectrum of anti-tumor activity [26,27]. We, therefore, believe that the full potential of low-dose gemcitabine in long infusion is yet to be defined. Still, looking at this trial, we have to admit that the contribution of an unconventional schedule of gemcitabine to the apparent superiority of the doublet is uncertain.

Our experience is in accordance with other trials on chemotherapy for patients with NSCLC in poor performance status. Even in this weak population of patients, treatment with low-dose platin-based doublets or non-platin doublets is feasible [28–34] and may be superior to monotherapy [35,36]. In our trial, a mild doublet of low-dose gemcitabine in long infusion and cisplatin was superior to the standard monotherapy with gemcitabine. Although toxicity was very mild and comparable, the patients treated with the doublet reported a better quality of life and had statistically significant higher response rate and longer survival.

Owing to the ageing population and time trends in the tobacco epidemics, we may excpect an increase in the proportion of elderly patients with lung cancer, including those with significant comorbidity. According to the Cancer Registry of Slovenia, the proportion of patients with lung cancer over 75 years of age increased from 14% in 1976 to 21% in 2006 [37]. It is clear, then, that this frail population of patients with lung cancer should be offered more attention in routine clinical practice and in clinical research. Our trial introduces a new piece into the mosaic of treatment options for patients with advanced NSCLC in poor performance status. In combination with cisplatin at 60 mg/m^2, gemcitabine in low dose in prolonged infusion is an effective treatment with very low toxicity and deserves to be considered both in daily routine and for future clinical trials.

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