Annals of Oncology 11: 821–827, 2000.

Original article

Phase I and pharmacologic study of weekly gemcitabine and paclitaxel in chemo-naïve patients with advanced non-small-cell lung cancer

T. De Pas,[1] F. de Braud,[1] R. Danesi,[2] C. Sessa,[3] C. Catania,[1] G. Curigliano,[1] S. Fogli,[2] M. del Tacca,[2] G. Zampino,[1] A. Sbanotto,[1] A. Rocca,[1] S. Cinieri,[1] E. Marrocco,[1] A. Milani[1] & A. Goldhirsch[1]

[1]*Divisions of Medical Oncology and Hemato-Oncology, European Institute of Oncology, Milano;* [2]*Department of Oncology, Division of Pharmacology, Pisa University, Italy;* [3]*Oncology Institute of Southern Switzerland, Bellinzona, Switzerland*

Summary

Background: Gemcitabine (GEM) and paclitaxel (TAX) are active, non-cross-resistant drugs in non-small-cell lung cancer (NSCLC). We performed a phase I study to determine the maximum-tolerated dose (MTD), antitumor activity and pharmacokinetics of GEM and TAX given weekly in chemo-naïve patients with advanced NSCLC.

Patients and methods: Escalating doses of GEM (800–2000 mg/m^2) and TAX (60–100 mg/m^2) were administered on days 1, 8, 15 every 4 weeks to 35 patients with advanced NSCLC. Plasma pharmacokinetics of TAX and GEM was assessed at the three higher dose-levels.

Results: Dose-escalation was discontinued in absence of MTD because of increased cumulative toxicity leading to dose modification or treatment delay at levels 6 and 7 (TAX 100 mg/m^2 plus GEM 1750 and, respectively, 2000 mg/m^2). Hematological toxicity included grade 4 neutropenia in 3% of cycles, grade 3 thrombocytopenia in one cycle and febrile neutropenia in three cycles. Maximal non-hemathological toxicity was grade 3 elevation in serum transaminases and grade 2 neuro-sensory toxicity in 8% and 5% of cycles, respectively. At the two higher dose-levels a non-linear pharmacokinetics of GEM was observed with a remarkable variability of C_{max} and AUC. No pharmacokinetic interactions were reported. Objectives responses were seen at all dose levels, with an overall response rate of 43% (95% confidence interval (95% CI): 25.5%–62.6%) in 30 evaluable patients.

Conclusions: The weekly administration of GEM and TAX is very well tolerated, and has shown promising antitumor activity in NSCLC. In view of the cumulative toxicity and of the pharmacokinetic profile of GEM, doses of 1500 mg/m^2 of GEM and 100 mg/m^2 of TAX are recommended for phase II studies.

Key words: gemcitabine, non-small-cell lung cancer, paclitaxel, pharmacokinetic

Introduction

Chemotherapy has been shown to improve both quality of life and survival in patients with advanced non-small-cell lung cancer (NSCLC) [1, 2].

Paclitaxel (TAX) and Gemcitabine (GEM) are both active as single agent in NSCLC with acceptable toxicity profiles. Cumulative data from several studies with TAX in advanced NSCLC patients showed a median response rate of about 25%, with a one-year survival rate of 41% [3]. A weekly schedule of TAX appeared active and well tolerated resulting in a higher dose-intensity and frequent exposure to the drug. The MTD in chemo-naïve patients was reached at 175 mg/mq/w for six weeks of an eight-week cycle, with acute dose-limiting neutropenia and cumulative peripheral neuropathy [4, 5].

The pharmacokinetic profile of one-hour infusion of TAX has been shown to be comparable to that of three-hour infusion with higher peak plasma levels, but similar toxicity and activity and no increase of hypersensitivity reactions in spite of the simplified regimen of prophylaxis adopted [6–10].

GEM is considered an active agent in NSCLC, with a cumulative response rate of 21% and a one-year survival of 39% among 572 patients [3]. The most extensively used regimen is the weekly 30-minute infusion for three consecutive weeks every four weeks.

The rationale of combining GEM and TAX for NSCLC is provided by their antitumor activity, different mechanism of cytotoxicity and different toxicity profiles. Three phase I–II studies of TAX plus GEM combinations have been performed on a total of one hundred both chemo-naïve and pretreated patients with advanced NSCLC [11–13], with an overall response rate of 29%–42%. In these studies TAX was administered every three weeks with escalation of the dose from 90 mg/m^2 to 240 mg/m^2 in two of them.

Only preliminary data in a still ongoing study with a weekly administration of GEM and TAX in patients with different solid tumors are available [14]. In the present study we wanted to evaluate the toxicity and antitumor activity of TAX and GEM given weekly as initial treatment in NSCLC patients. Pharmacokinetic and pharmacodynamic evaluations of GEM and TAX were performed at the higher dose levels.

Patients and methods

Eligibility criteria

Chemo-naïve patients with histologically or cytologically proven stage IIIb–IV NSCLC were eligible for this study. Additional eligibility criteria were adequate bone marrow (WBC $\geq 3500/\mu l$ and platelet count $\geq 100{,}000/\mu l$), hepatic (AST, ALT ≤ 2 times and total bilirubin ≤ 1.25 times upper limits of normal) and renal (serum creatinine ≤ 1.25 times upper limits of normal) functions, 18–65 years of age, performance status (ECOG) ≤ 2, ≥ 3 months of life expectancy, written informed consent. Exclusion criteria were a prior radiotherapy to more than 30% of bone marrow reserve, absolute contraindication to steroids, previous or concurrent malignancies, uncontrolled infections. The protocol was approved by the local ethical committee.

Pretreatment evaluation

Pretreatment evaluation included complete history and physical examination, complete blood cell count, a full chemistry profile, ECG, chest X-ray and CT scan, abdomen CT scan or ultrasound and bone scan. During treatment a weekly complete blood cell count and a complete chemistry profile on the first day of each treatment were performed.

Treatment schedule, toxicity and response evaluation

The dose-escalation schedule is listed in Table 2. TAX and GEM were administered weekly on an outpatient basis for three consecutive weeks every 28 days. TAX was administered as a one-hour i.v. infusion after prophylactic premedication with prednisone 25 mg orally 12 hours and hydrocortisone 200 mg plus ranitidine 100 mg plus clorfenamine 10 mg i.v. 1 hour before treatment.

GEM was administered immediately after TAX as a 30-minute i.v. infusion. One cycle of treatment consisted of three consecutive weekly administrations of TAX and GEM followed by one week of rest.

All patients with measurable disease underwent complete tumor-response assessment after two cycles. WHO response criteria were used [15]. Four to eight cycles were planned according to physician's discretion in both responders and in patients with stable-disease.

Toxicity was evaluated according to WHO criteria.

Treatment was repeated on day 28 if absolute neutrophils (ANC) and platelets were $\geq 1.5 \times 10^3/\mu l$ and $\geq 100 \times 10^3/\mu l$, respectively, and in presence of non-hematological toxicity $\leq$G1 (hepatic toxicity $\leq$G2). Otherwise, treatment was delayed for one week and, if these conditions were still not satisfied on day 35, discontinued and toxicity considered to be dose-limiting. Treatment administration was given on day 8 and 15 if ANC and platelets were $\geq 1{,}0 \times 10^3/\mu l$ and $\geq 75 \times 10^3/\mu l$, respectively, with non-hematological toxicity $<$G2 (excluding nausea/vomiting and alopecia). Otherwise, treatment was discontinued and toxicity considered to-be dose-limiting.

Quality of life was assessed weekly by the EORTC QLQ-C30 and LC-13. We used a linear mixed effect model to investigate if the quality of life scores were the same over time to take into account the repeated observations on each subject [16]. We permitted the intercept and slope to vary according to each subject. The within subject correlation matrix was taken to be the identity matrix as there was no evidence of any serial correlation in the within subject residuals over time.

Dose finding procedures and DLT

At each dose level three patients, six in case of dose-limiting toxicity (DLT) were entered. The maximum tolerated dose (MTD) was defined as the dose level at which DLT was observed in two out of three or in three out of six patients during the first cycle. DLTs were an ANC of $<0.5 \times 10^3/\mu l$ lasting ≥ 7 days, febrile neutropenia (fever $\geq$ 38.5 °C with G4 neutropenia or febrile G3 neutropenia requiring i.v. antibiotics or hospitalization); platelets $<25 \times 10^3/\mu l$, neurotoxicity $>$G2, mucositis $>$G2; treatment withheld because of toxicity on days 8 or 15 or a treatment delay of >1 week on day 28.

Dose intensity

Dose intensity (DI) ($mg/m^2/wk$) was calculated by the following formula: total milligrams of drug per body surface areas/total days of therapy/7, where total days is the number of days between day one of the first cycle and day 28 of the last one.

Pharmacokinetic and pharmacodynamic analysis

Pharmacological evaluations were performed on patients treated with GEM at 1500, 1750 and 2000 mg/m^2 in association with TAX 100 mg/m^2. Blood samples were drawn from the arm not receiving the infusion before treatment (baseline), 15 minutes and 1 hour after the start of TAX infusion, 5 and 30 minutes after the start of GEM infusion and 5, 15, 30 minutes and 1, 2, 4, 12, 24 hours after it. Samples were centrifuged for 10 minutes at 3,500 g and stored at −20 °C. Plasma levels of TAX, GEM and its metabolite 2',2'-difluorodeoxyuridine (dFdU) were determined by a high performance liquid chromatographic assay previously described [17, 18]. Pharmacokinetic analysis was performed by a Kinfit module incorporated in the MW/PHARM computer program [19] (Mediware, Groningen, The Netherlands) and drug disposition was fitted to an open two compartment linear model. The area under the plasma concentration-time curve (AUC) was calculated using a combination of the linear and log trapezoidal rules extrapolated to infinity. The pharmacokinetic study of TAX included the measurement on individual plasma concentration-time plots of the time spent above the threshold level of 0.05 μmol/l ($tC_{0\,05}$) [20]. Pharmacodynamic correlations between the percentage decrease in absolute leucocyte, neutrophil and platelet count defined as: 100 × (pre-treatment value − nadir value)/pre-treatment value and C_{max} and AUC of TAX and GEM, and time of plasma concentrations above 0.05 μmol/l of TAX were assessed. These relationships were fitted to sigmoidal maximum effect (E_{max}) models [21] using nonlinear least squares regression and a weighting factor of unity (GraphPad Prism, GraphPad Software, USA).

Pharmacokinetic differences were analyzed by the unpaired t-test [22].

Results

Patient characteristics

Between November 1997 and March 1999, 35 consecutive patients entered the study (Table 1). All patients were assessable for toxicity and 30 for response because of lack of measurable disease in 5.

Dose levels and toxicity

The doses of GEM and TAX were escalated from 800 to 2000 mg/m^2 and from 60 to 100 mg/m^2, respectively, through 7 dose levels; a total of 143 treatment cycles were administered, 111 of them at full dose, all evaluable for toxicity (Table 2).

DLT, hematological, and hepatic toxicity

A total of six DLTs, all hematological, were registered, five of which at the three highest dose levels. DLTs during the first cycle consisted of G3 and G2 thrombocyto-

Table 1. Patients' characteristics (n = 35).

Characteristic	Number of patients
Age (years)	
Median	54
Range	36–73
Sex	
Male	22
Female	13
Performance status (ECOG)	
0–1	35
Stage	
IIIB	2
IV	33
Prior radiation	7
Histology	
Adenocarcinoma	19
Large cell	3
Squamous cell	7
Poorly diff. ca	6
Main sites of disease	
Lung	33
Liver	8
Brain	6
Bone	16

Table 2. DLT at first cycles and reasons of treatment delay or dose-modifications over all 143 cycles.

Dose level	GEM (mg/m^2)	TAX (mg/m^2)	No. of pts	Dose limiting toxicity (n)	Reason of delay or modification (n) all cycles
1	800	60	3	–	Taxol allergic reaction (1)
2	800	80	4	–	Pneumonitis (1)
3	1000	80	6	G3 thrombocytopenia day 15 (1)	Transaminitis (1)
4	1000	100	3	–	Neurotoxicity (1)
5	1500	100	7	G2 thrombocytopenia day 15 (1) Neutropenic fever (1)	Herpes zoster (1) Neurotoxicity (1)
6	1750	100	6	Neutropenic fever (2)	Neurotoxicity (2) Transaminitis (1) Taxol allergic reaction (1)
7	2000	100	6	G4 neutropenia day 15 (1)	Transaminitis (2) Neurotoxicity (1) Astenia (1)

penia on day 15, with recovery within a week, in one of six and in one of seven patients. treated at dose level 3 and 5, respectively, of neutropenic fever requiring i.v. antibiotics in a different patient treated at the dose level 5, in two of six patients at dose level 6, and of G4 neutropenia on day 15, with recovery within a week, in one of six patients at dose level 7. The main reason for treatment delay or modification of the dose was cumulative neurotoxicity (five patients) and hepatotoxicity (four patients). Hepatic toxicity was limited to elevations in serum transaminases, always asymptomatic and reversible.

Table 3 reports the incidence of grade 3–4 neutro-thrombocytopenia and elevation in serum transaminases during the first and all cycles.

Neutropenia was dose-dependent: all G4 neutropenia episodes but one occurred at dose levels 6 and 7, where a 16% and 10%, respectively, of incidence of G3–G4 neutropenia among all cycles was registered. Grade 3 thrombocytopenia occurred in only one case at dose level 3. Elevation of hepatic transaminases occurred at all levels but the first but it was not either dose-dependent or cumulative. It was G2 in 50%–100% of patients at all levels and G3 in 20% of cycles at the highest dose level. At this dose, however, two of six patients were retreated at dose level 6 because of elevation of hepatic transaminases.

Other non-hematological toxicities

Other non-hematological toxicity, including nausea and vomiting, mucositis, diarrhea and neuro-sensory peripheral neuropathy, were always mild to moderate and non-cumulative; they were not clearly dose-dependent but were more frequent at the highest dose level (Table 4), at which two patients were retreated at the lower dose of GEM because of asthenia and, respectively, neurotoxicity. Neurotoxicity consisted in extremities paresthesias and/or dysesthesia, always reversible after treatment interruption.

Complete alopecia occurred in six patients, three of whom at dose level 7.

Transient flu-like syndrome consisting of low-grade fever, myalgias and fatigue, was reported in seven patients. It was responsive to acetaminophen and not dose dependent.

Two allergic reactions was registered, one of them with dyspnoea and bronchospasm, requiring treatment interruption. The same reaction was observed when the patient received cisplatin plus GEM.

Quality of life

For the EORTC QLQ-C30 there was no evidence of any trend in the scores (P = 0.5). There was evidence that the LC-13 scores increased within subject over time (P = 0.01). The increase is estimated at 0.3 (95% CI: 0.08–0.53) points per week. Patients whose treatment terminated early tended to have a high LC-13 score prior to ceasing treatment. Patients who remained on treatment for more than eight administrations tended to have low LC-13 scores throughout the treatment period.

Dose-intensity

The results of the analysis of the delivered dose intensity, of both drugs over all cycles of treatment are summarized in Table 5.

According to this analysis, which takes into account

Table 3. First cycles and overall grade 3–4 hematological toxicity and elevation of hepatic transaminases.

Level	Number of patients/cycles	Percentage of cycles with neutropenia				Percentage of cycles with thrombocytopenia				Percentage of cycles with elevation of hepatic transaminases			
		First (n = 35)		All (n = 111)		First (n = 35)		All (n = 111)		First (n = 35)		All (n = 111)	
		3	4	3	4	3	4	3	4	3	4	3	4
1	3/7	0	0	0	0	0	0	0	0	0	0	0	0
2	4/17	25	0	29	0	0	0	0	0	0	0	0	0
3	6/21	0	0	5	5	17	0	5	0	33	0	19	0
4	3/10	0	0	10	0	0	0	0	0	0	0	0	0
5	7/23	14	0	43	0	0	0	0	0	0	0	0	0
6	6/13	17	17	8	8	0	0	0	0	0	0	0	0
7	6/20	17	17	5	5	0	0	0	0	33	0	20	0

Table 4. Other non-hematological toxicity.

Level	Number of patients/cycles	Cycles with nausea/vomiting (%)		Cycles with mucositis (%)		Cycles with neuro-sensory toxicity (%)		Cycles with diarrhea (%)	
		1	2	1	2	1	2	1	2
1	3/7	57	14	0	0	0	0	0	0
2	4/17	29	0	0	6	6	0	18	0
3	6/21	24	0	19	0	0	0	9	0
4	3/10	30	0	20	10	10	10	20	10
5	7/23	48	0	4	39	39	8	0	0
6	6/13	15	8	23	23	23	8	8	0
7	6/20	25	20	25	35	35	10	5	0

Table 5. Scheduled vs. delivered percent dose intensity for paclitaxel and gemcitabine over all cycles.

Dose level	Scheduled GEM–TAX dose (mg/mq)	Delivered GEM (% dose)	Delivered TAX (% dose)	Delivered GEM and TAX cumulative % dose over all the cycles of therapy
1	800–60	93	93	93
2	800–80	98	98	98
3	1000–80	96	96	96
4	1000–100	98	96	97
5	1500–100	86	91	88
6	1750–100	88	79	83
7	2000–100	90	89	89

the dose reductions for each drug as well as any delays in drug administration, the actual dose intensities of TAX and GEM delivered were lower than 85% only for dose level 6.

The average dose intensity administered was higher for dose levels from 1 to 5 (94.5%) than for dose levels 6 and 7 (86.4%), due to the more frequent dose reductions and dose delays due to toxicity.

Pharmacokinetic and pharmacodynamic analysis

In patients given GEM 1500, 1750 and 2000 mg/m^2, the mean C_{max} values of TAX at the end of infusion were 9.10 ± 2.27, 8.96 ± 1.28 and 8.94 ± 4.09 μmol/l. Plasma concentrations decreased in the post-infusion period by a bi-exponential decay with comparable pharmacokinetic profiles at the three dose levels of GEM. The TAX AUC at the three different dose levels were also comparable, with concomitant total clearance values of 7.61 ± 1.81, 8.25 ± 2.97 and 8.57 ± 2.62 l/h/m^2, thus indicating that dose-escalation of GEM did not affect TAX disposition.

Peak plasma levels of GEM were reached at the end of infusion and increased from 18.56 ± 2.85 to 40.85 ± 14.85 and the AUC values increased from 9.99 ± 1.59 to 25.01 ± 9.87 μg/ml/h from 1500 to 2000 mg/m^2. According to these results, increasing the dose of GEM by 17% and 33% from 1500 mg/m^2 resulted in a mean increase of 27% and 120% of C_{max} and of 32% and 150% of AUC. These data suggest a saturable kinetics of GEM within the dose range administered. This observation is also supported by the observed significant decrease of the total clearance of GEM for doses of 1500 mg/m^2 and, respectively, 2000 mg/m^2 of 160.4 ± 22.0 l/h/m^2 and 92.5 ± 38.9 l/h/m^2.

Accordingly, the pharmacokinetics of dFdU was linearly related to the dose of GEM with C_{max} values of 63.2 ± 9.7, 70.6 ± 19.0 and 79.7 ± 15.3 μg/ml and AUC of 159.9 ± 46.2, 182.0 ± 49.0 and 224.9 ± 61.5 μg/ml/h at 1500, 1750 and 2000 mg/m^2 dose levels, respectively.

The analysis of the correlation between pharmacokinetics and drug effect demonstrated that percentage decrease in ANC was related to the time of exposure to TAX concentrations $\geq$0.05 μmol/l, as described by the sigmoid maximum effect (E_{max}) pharmacodynamic model (r^2 = 0.63). The comparison with historical data [20] indicated that the duration of plasma concentrations above the threshold value of TAX 0.05 μmol/l predicted to yield a 50% reduction in ANC were 10.4 hours and, approximately, 17 hours in patients treated with TAX–GEM and TAX alone, respectively. This suggests that patients receiving TAX and GEM experi-

Table 6. Pharmacokinetic parameters (mean ± SD) of TAX, GEM and dFdU.

Parameter	TAX			GEM			dFdU		
Gemcitabine dose (mg/m^2)	1500	1750	2000	1500	1750	2000	1500	1750	2000
Paclitaxel dose (mg/m^2)	100	100	100	100	100	100	100	100	100
C_{max}[a]	9.10 ± 2.27	8.96 ± 1 28	8.94 ± 4.09	18.56 ± 2.85	23.56 ± 4.08	40.85 ± 14.85	63.2 ± 9.7	70.6 ± 19.0	79.7 ± 15.3
AUC[b]	13.86 ± 4.07	14.45 ± 2.03	12.73 ± 4.22	9.99 ± 1.59	13.21 ± 2.20	25.01 ± 9.87	159.9 ± 46.2	182.0 ± 49.0	224.9 ± 61.5

[a] C_{max}: TAX – μmol/l; GEM and dFdU – μg/ml.
[b] AUC: TAX – μmol/l/h; GEM and dFdU – μg/ml/h.

Table 7. Antitumor activity.

Level	Number of assessable patients	CR	PR	SD	PD	RR (%)
1	3	0	2	0	1	67
2	4	0	3	0	1	75
3	4	0	1	0	3	25
4	3	0	0	1	2	–
5	5	0	2	1	2	40
6	6	0	2	1	3	33
7	5	0	3	2	0	60
All	30	0	13	5	12	43[a]

[a] 95% CI: 25.5–62.6.

enced more neutropenia than would be expected from TAX alone.

In the analysis of the relationship between haematological toxicity and pharmacokinetics of GEM only the percentage decrease in platelets appeared to be related to the C_{max} of GEM through sigmoid E_{max} pharmacodynamic model relationship (r^2 = 0.76). The sigmoid curve of C_{max} and percentage decrease in platelets reached a plateau for a percentage decrease in platelets of 58.7% (95% CI: 46.3%–71.1%).

Antitumor activity

Antitumor activity was evaluated in all 30 patients with measurable disease treated with at least 2 cycles of chemotherapy (Table 7). Responses were seen at all dose levels, with no clear evidence of a dose–response relationship. Thirteen out of thirty assessable patients (43%; 95% CI: 25.5%–62.6%) achieved a partial response, five had stable disease and twelve had disease-progressions. Median time to progression was 15.8 weeks (range 6.7–56 weeks).

A median of 5 courses (range 2–6) were given to responding patients, with response noted after a median of 2 courses (range 2–6).

Discussion

We performed a dose-finding study to define the maximal tolerated dose (MTD) of gemcitabine (GEM) and paclitaxel (TAX) given weekly for three consecutive weeks followed by one-week rest in chemo-naïve patients with advanced NSCLC. Seven dose-levels were evaluated, with TAX dose escalated from 60 mg/m^2 to 100 mg/m^2/w and GEM from 800 mg/m^2 to 2000 mg/m^2/w.

Dose escalation was discontinued after doses of TAX and GEM of 100 mg/m^2 and, respectively, 2000 mg/m^2 because four out of six patients treated at this dose-level had neurotoxicity, asthenia or hepatotoxicity requiring a decrease of GEM dose to dose level 6 and three patients developed G3 transaminitis. Consequently, even though the criteria of MTD were not satisfied because only one patient treated at the higher level experienced a DLT (G4 neutropenia in day 15), the study was closed and weekly doses of 100 mg/m^2 TAX and 1500 mg/m^2 GEM were proposed for further clinical evaluation.

The main DLT was myelosuppression, with G2–3 thrombocytopenia on day 15 in 2 patients, G4 neutropenia on day 15 in 1 patient and neutropenic fever requiring i.v. antibiotics in 3 patients out of 35 patients treated. Fourteen patients had treatment delays or modifications due to non-hematological toxicities, namely neurotoxicity in five patients and transaminitis in four patients.

The patients compliance to this schedule was excellent. Grade 2 alopecia occurred in 14% of patients while the only G3 non-hematological toxicity consisted of asymptomatic reversible rising of transaminases (8% of cycles). Two allergic reactions were registered, one of them with dyspnea and asthmatic phenomena requiring treatment interruption. Grade 2 neuro-sensory toxicity occurred in 6 out of 35 patients and it was always reversible.

The analysis of the quality of life data supports the view that this regimem is well tolerated, with stable trends in QLQ-C30 scores.

In the present study GEM displayed a linear pharmacokinetics up to 1500 mg/m^2, after which a non-linear pharmacokinetic behavior and a higher interpatient variability of C_{max} and AUC were reported.

The pharmacokinetics achieved in the present study indicate that TAX disposition is not affected by GEM administered at doses between 1500 and 2000 mg/m^2 as suggested by the comparison with previous results achieved with TAX single agent [23, 24]. The present data confirm he results of Kroep et al. of no interactions between GEM and TAX in patients receiving fixed doses of both drugs given intermittently on a three-week schedule [25].

Percentage decrease in platelets appeared to be related to C_{max} of GEM (r^2 = 0.76) and the highest percentage

decrease of 58.7% was achieved for a GEM C_{max} of 18 μg/ml, after which a further increase of C_{max} did not result in a higher percentage decrease in platelets.

In the present study, thrombocytopenia was of lower degree as compared to the one observed in a phase I of GEM with 50% of patients experiencing nadir platelet values of less than 50,000 cells/mm^3 at 1000 mg/m^2/w [17]. Thrombocytopenia was not observed also on patients treated with single agent TAX 100 mg/m^2/h [23], and a positive pharmacodynamic interaction between TAX and GEM might be considered. However the lack of cellular pharmacology of dFdCTP, the cellular C_{max} of which was shown to be affected in a dose-dependent manner by TAX [25] do not allow a more extensive comparison with other TAX and GEM studies.

Overall the pharmacokinetic results suggest an increasing risk of possible unpredictable side-effects at the higher treatments levels, consistent with the cumulative toxicity and the higher number of patients requiring treatment modification at dose levels 6 and 7.

Major responses were observed at all the treatment levels with 13 partial responses (overall response 43%, 95% CI: 25.5%–62.6%), 5 stable disease and 12 disease progression among the 30 evaluable patients. Median time to progression was 15.8 weeks (range 6.7–56 weeks).

The lack of dose-response relationship and of linearity of GEM pharmacokinetics at the higher doses were additional rationale to decide discontinuing dose escalation.

Although TAX is not rarely administered at 200–250 mg/m^2, its dose-response relationship is still matter of debate and advantages of administering doses higher than 125–150 mg/m^2 every three weeks have not been conclusively proven [26, 27]. Also for GEM a clear dose-response relationship for weekly doses higher than 900–1250 mg/m^2 is still unproved [28–34].

The favorable toxicity profile and the promising antitumor activity reported in the present study in chemonaïve patients with NSCLC support further clinical evaluation of GEM and TAX given in combination at 1500 mg/m^2 and, respectively, 100 mg/m^2 weekly, for three consecutive weeks.

References

1. Non-Small-Cell Lung Cancer Collaborative Group. Chemotherapy in non-small-cell lung cancer: A meta-analysis using updated data in individual patients from 52 randomized clinical trials. BMJ 1995; 311: 899–909.
2. Marino P, Pampallona S, Preatoni A. Chemotherapy *versus* supportive care in advanced non-small cell lung cancer: Results of a meta-analysis of the literature. Chest 1994; 106: 861–5.
3. Bunn PA Jr, Kelly K. New chemotherapeutic agents prolong survival and improve quality of life in non-small-cell lung cancer: A review of the literature and future directions. Clin Cancer Res 1998; 1087–100.
4. Akerley W, Glantz M, Choy H et al. Phase I trial of weely paclitaxel in advanced lung cancer. J Clin Oncol 1998; 16: 153–8.
5. Chang A, Boros L, Asbury R et al. Weekly moderate-dose Paclitaxel in stage IV non-small cell lung cancer. Proc Am Soc Clin Oncol 1998; 17 (Abstr 1806).
6. Eisenhauer EA, Huinink HB, Swenerton KD et al. European-Canadian randomized trial of Taxol in relapsed ovarian cancer: High- *versus* low-dose and long vs. short infusion. J Clin Oncol 1994; 12: 2654–66.
7. Hainswort JD, Thompson DS, Greco FA. Paclitaxel by one-hour infusion: An active drug in metastatic non-small-cell lung cancer. J Clin Oncol 1995; 13 (7): 1609–14.
8. Mross K, Hauns B, Haring B et al. Clinical phase I study with one-hour paclitaxel infusion. Ann Oncol 1998; 9: 569–72.
9. Greco FA, Hainswort JD. Paclitaxel via one-hour infusion: Rationale and pharmacology. Semin Oncol 1996; 23 (Suppl 15): 19–20.
10. Greco FA, Hainswort JD. Paclitaxel via one-hour infusion: Clinical experience. Semin Oncol 1996; 23 (Suppl 16): 91–3.
11. Georgoulias V, Kourousis C, Kakolyris S et al. Second-line treatment of advanced non-small cell lung cancer with paclitaxel and gemcitabine: A preliminary report on an active regimen. Semin Oncol 1997; 24 (4, Suppl 12): S61–6.
12. Giaccone G, Smit E, Laan D et al. Phase I–II study of paclitaxel and gemcitabine in advanced non-small-cell lung cancer. Proc Am Soc Clin Oncol 1998; 17 (Abstr 1869).
13. Tortoriello A, Facchini G, Caponigro F. Gemcitabine plus paclitaxel in non-small-cell lung cancer. Preliminary data of a phase I–II study. Paris: Proc 7 International Congress Anti-Cancer Treatment 1997 (Abstr 434).
14. Sandler A, Raghavan D, Meropol N et al. A phase I trial of gemcitabine plus paclitaxel combination therapy in patients with refractory solid tumors. EJC, ECCO 1997; S248 (Abstr 1120).
15. Beacon HJ. Thompson SG. Multi-level models for repeated measurement data: Application to quality of life data in clinical trials. Stat Med 1996; 15 (24): 2717–32.
16. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. WHO Offset Publication No. 48. Geneva: WHO 1979.
17. Abbruzzese JL, Grunewald R, Weeks E et al. A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. J Clin Oncol 1991; 15: 491—8.
18. Sharma A, Conway WD, Sraubinger RM. Reversed-phase high-performance liquid chromatographic determination of Taxol in mouse plasma. J Chromatogr B Biomed Appl 1994; 655: 315–9.
19. Proost JH, Meijer DKF. MW/PHARM, an integrate software package for drug dosage regimen calculation and therapeutic drug monitoring. Comput Biol Med 1992; 22: 155–63.
20. Gianni L, Kearns CM, Giani A et al. Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in human. J Clin Oncol 1995; 13: 180–90.
21. Rowland M, Tozer TN. Clinical Pharmacokinetics: Concepts and Applications (3rd edition). Baltimore, Maryland: Williams & Wilkins 1995.
22. Zar JH. Biostatistical Analysis. Englewood Cliffs, New Jersey: Prentice Hall 1984.
23. Seidman AD, Hudis CA, McCaffrey J et al. Dose-dense therapy with paclitaxel via weekly one-hour infusion: Toxicity and pharmacokinetics. Semin Oncol 1997; 24 (Suppl 17): 72–6.
24. Maier-Lenz H, Hauns B, Haering B et al. Phase I study of paclitaxel administered as one-hour infusion: Preliminary experience in the treatment of metastatic breast cancer. Semin Oncol 1997; 24 (Suppl 19): 16–9.
25. Kroep JR, Giaccone G, Voorn DA et al. Gemcitabine and paclitaxel: Pharmacokinetic and pharmaco-dynamic interactions in patients with non-small-cell lung cancer. J Clin Oncol 1999; 17: 2190–7.
26. Nabholtz J, Gelman K, Bontembal M et al. Multicenter randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol 1996; 14: 1858–67.
27. Bonomi P, Kim K, Chang A et al. Phase III trial comparing etoposide–cisplatin *versus* Taxol with cisplatin–G-CSF *versus* Taxol–cisplatin in advanced non-small-cell lung cancer. An

Eastern Cooperative Oncology Group (ECOG) trial. Proc Am Soc Clin Oncol 1996; 15 (Abstr 1145).
28. Fossella F, Lippman S, Shin D et al. Maximum-tolerated dose defined for single-agent gemcitabine: A phase I dose-escalation study in chemotherapy-naïve patients with advanced non-small-cell lung cancer. J Clin Oncol 1997; 15: 310–6.
29. Abratt RP, Bezwoda WR, Falkson G et al. Efficacy and safety profile of gemcitabine in advanced non-small-cell lung cancer: A phase II study. J Clin Oncol 1994; 12: 1535–40.
30. Anderson H, Lund B, Bach F et al. Single-agent activity of weekly gemcitabine in advanced non-small-cell lung cancer: A phase II study. J Clin Oncol 1994; 12: 1821–6.
31. Fukuoka M, Kruita Y, Niitani H. Gemcitabine in non-small-cell lung cancer: The Japanese experience. Presented at the 7th World Conference on Lung Cancer Mini-Symposium, 'Efficacy, symptomatology and cost as decision points in lung cancer treatment: Investigational experience with gemcitabine'. Colorado Springs, Colorado, June 26, 1994.
32. Nakai Y, Takada M, Yokoyama A et al. Results of phase II studies of gemcitabine in patients with non-small-cell lung cancer in Japan. Lung Cancer 1994; 11 (Suppl 1): 120 (Abstr 460).
33. Le Chevalier T, Gottfried M, Gatzemeier U et al. Confirmatory activity of gemcitabine in non-small-cell lung cancer. Eur J Cancer 1993; 29A (Suppl 6): S160 (Abstr 882).
34. Kassem B, Miketic LM, Landreneau RJ et al. Phase I studty of gemcitabine given weekly as short infusion. Proc Am Soc Clin Oncol 1995; 14: 383 (Abstr 1190).

Received 27 March 2000; accepted 10 May 2000.

Correspondence to:
T. De Pas, MD
Division of Medical Oncology
European Institute of Oncology
Via Ripamonti, 435
20141 Milan
Italy
E-mail: tommaso.de-pas@ieo.it