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ORIGINAL ARTICLE

# A dose escalation and pharmacokinetic study of the biweekly administration of paclitaxel, gemcitabine and oxaliplatin in patients with advanced solid tumors

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**Abstract**
*Purpose* To determine the dose-limiting toxicities (DLTs) and the maximum tolerated doses (MTDs) of the paclitaxel, gemcitabine, oxaliplatin combination administered biweekly in patients with advanced solid tumors.
*Patients and methods* Patients received escalated doses of paclitaxel (starting dose: 100 mg/m$^2$), gemcitabine (starting dose: 800 mg/m$^2$) and oxaliplatin (starting dose: 50 mg/m$^2$) on days 1 and 15 in cycles of every 4 weeks. DLTs were evaluated during the first cycle.
*Results* Twenty-seven patients (median age 65 years) with performance status 0–1 were treated on six dose escalation levels. Eleven patients (40.7%) were chemotherapy naïve, six (22.2%) had received 1 prior chemotherapy regimen and ten (37.1%) 2 or more. The DLT level was reached at the doses of paclitaxel 110 mg/m$^2$, gemcitabine 1,150 mg/m$^2$ and LOHP 70 mg/m$^2$. The dose-limiting events were grade 4 neutropenia and grade 3 febrile neutropenia. Neutropenia was the most common adverse event. A median of 3 cycles per patient was administered. One complete and five partial responses were observed in patients with ovarian carcinoma, NSCLC, urothelial cancer, mesothelioma and cancer of unknown primary. No pharmacokinetic drug interactions were detected.
*Conclusions* The recommended doses for future phase II studies of this combination are paclitaxel 110 mg/m$^2$, gemcitabine 1,000 mg/m$^2$ and oxaliplatin 70 mg/m$^2$ every 2 weeks. The regimen is generally well tolerated and merits further evaluation.

**Keywords** Paclitaxel · Gemcitabine · Oxaliplatin · Phase I · Solid tumors · Pharmacokinetic

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## Introduction

In general, combination chemotherapy offers longer time to tumor progression (TTP) and higher response rates, but the lack of a clear benefit in overall survival and the associated greater toxicity makes it one of the most debatable subjects in the treatment of metastatic disease [1]. Nevertheless, in a number of solid tumors such as gynecologic malignancies and lung cancer, combinations of platinum compounds with taxanes are widely used, mainly because of their strong synergy [2, 3].

Paclitaxel is one of the most active chemotherapeutic agents in various tumors. However, the optimal dose and administration schedule are not yet fully defined. It seems that instead of the conventional triweekly administration, the more frequent administration (weekly or biweekly) is feasible and associated with acceptable toxicity, improved tolerance and increased activity [4–6].

Oxaliplatin (LOHP) has shown activity in a wide range of solid tumors including colorectal, ovarian, breast cancer and gastrointestinal tumors [7–9]. It is only partially cross-resistant with carboplatin and cisplatin and lacks the severe hematologic toxicity of the first and the nephrotoxicity and ototoxicity of the second [10]. The dose-limiting toxicity (DLT) of LOHP is transient sensory neuropathy which is

manifested as paresthesia and dysesthesia in the extremities and is generally reversible after discontinuation of treatment, although dose reductions or treatment omissions are sometimes necessary [7, 11]. The LOHP/paclitaxel combination has been shown to be active both in vitro and in vivo [12, 13].

Gemcitabine is an antimetabolite that inhibits DNA synthesis and blocks DNA repair pathways. This modulation of DNA repair pathways may be useful in overcoming platinum resistance [14]. Gemcitabine has demonstrated significant activity in a number of solid tumors, including gynecologic malignancies [15]. The LOHP/gemcitabine combination has been shown to be synergistic in vitro [16] and in vivo; phase I and II studies have shown that this combination is well tolerated with manageable toxicity and promising activity [8, 14, 17].

Based on the different mechanisms of action, in vitro synergism and non-overlapping toxicity profiles, the combined administration of paclitaxel, gemcitabine and LOHP constitutes an engaging regimen with theoretical and clinical supportive background. Since bone marrow recovery from chemotherapy-induced toxic effects usually occurs within 2 weeks, the biweekly administration schedule has been introduced, and has recently become very popular, as a means to increase dose density and, at the same time, deliver higher cumulative drug doses without excessive toxicity [18]. This phase I study was designed to evaluate the safety and tolerance of the triple combination of paclitaxel, gemcitabine and LOHP administered biweekly in patients with advanced solid tumors.

## Patients and methods

### Patient selection

Patients with histologically or cytologically confirmed advanced stage solid tumors, for whom there was no other proven effective treatment, were eligible for the study. Prior radiotherapy (to less than 25% of bone marrow containing bones) and chemotherapy were allowed but with a treatment-free interval of at least 4 weeks before entering the study. Other eligibility criteria were as follows: age 18–75 years, performance status (WHO) 0–2, life expectancy of at least 3 months, adequate bone marrow (absolute neutrophil count $\geq 1.5 \times 10^9\,l^{-1}$ and platelets $\geq 100 \times 10^9\,l^{-1}$), renal (creatinine $\leq$1.25 times the upper limit of normal and creatinine clearance >50 ml/min) and liver (total bilirubin $\leq$1.25 times and aspartate and alanine aminotransferases $\leq$3.0 times the upper limit of normal) function, absence of active infection and malnutrition (loss of more than 20% of the body weight). Patients with brain metastases were eligible if they had been irradiated, the brain lesions were radiologically stable and clinical improvement was evident. Patients with severe cardiac dysfunction and NCI-CTC peripheral neuropathy grade 1 or more were excluded from the study. The presence of measurable disease was not required. All patients gave their written informed consent. The study was approved by the Ethics and Scientific Committees of our Institution.

### Pretreatment and follow-up evaluation

Pretreatment evaluation included a detailed medical history and physical examination, a complete blood cell count (CBC) with differential and platelet count, whole blood chemistry, electrocardiograph (ECG) and computed tomography scans (CT) of the chest and abdomen and a whole body bone scan. Pretreatment evaluation had to be performed within 2 weeks prior to study entry.

During treatment, a CBC was performed weekly and in cases of grade 3–4 neutropenia, thrombocytopenia or febrile neutropenia daily until hematologic recovery. In addition, before each treatment cycle, routine biochemical tests and clinical assessment of the patients were performed. Response to treatment was evaluated after every 3 cycles or sooner if there was clinical evidence of disease progression. Although patients were not required to have measurable disease to enter the study, for those who did, tumor response was assessed using the RECIST criteria [19].

### Treatment

Paclitaxel was given at escalated doses starting from 100 mg/m$^2$ with increments of 10 mg/m$^2$ as a 3-h i.v. infusion followed by gemcitabine (Gemzar, Eli Lilly, Indianapolis, USA) at escalated doses starting from 800 mg/m$^2$ with increments of 200 mg/m$^2$ as a 30-min i.v. infusion and, last, LOHP (Eloxatin, Sanofi-Aventis, Bridgewater, USA) at escalated doses starting from 50 mg/m$^2$ with increments of 10 mg/m$^2$ as a 4-h i.v. infusion on days 1 and 15. Routine antiemetic prophylaxis with a 5-hydroxytryptamine-3-receptor antagonist was used. Premedication for paclitaxel consisted of methylprednisolone 16 mg orally 12 and 4 h and ranitidine 300 mg i.v. 30 min prior to infusion. Cycles were repeated every 4 weeks and treatment was administered until maximum response, disease progression, unacceptable toxicity or until the patient declined further treatment.

Patients were assessed for toxicity before each treatment administration using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 [20]. Chemotherapy was delayed until recovery if neutrophils were less than $1.5 \times 10^9\,l^{-1}$ or platelets less than $100 \times 10^9\,l^{-1}$ or for significant persisting non-hematologic toxicity. Patients who developed grade 4 neutropenia, grade 4 thrombocytopenia or febrile neutropenia were subsequently treated with the doses of the previous dose level. No prophylactic

administration of granulocyte colony-stimulating factor (G-CSF) was allowed. G-CSF was used for the treatment of febrile neutropenia. Neurologic adverse effects were assessed using the neurosensory scale of the NCI-CTC criteria. LOHP dose was reduced by 25% in cases of ≥grade 2 neurotoxicity lasting less than 14 days. In case of persistent (≥14 days) painful paresthesia or functional impairment, LOHP was omitted in subsequent cycles from the regimen until recovery. Patients requiring more than a 3-week treatment delay for any reason were withdrawn from the study. All patients who received at least one treatment administration were assessed for toxicity.

### Dose escalation

Dose escalation was performed according to the modified Fibonacci method. The following dose levels for paclitaxel/gemcitabine/LOHP have been evaluated: 100/800/50 (mg/m$^2$); 100/800/60 (mg/m$^2$); 100/1,000/60 (mg/m$^2$); and 110/1,000/60 (mg/m$^2$); 110/1,000/70 (mg/m$^2$); 110/1,150/70 (mg/m$^2$). No intra-patient dose escalation was allowed. Initially, three patients were enrolled at each dose level. If a DLT was observed in one of the first three patients, then three additional patients were enrolled at the same dose level.

The DLTs were assessed during the first cycle of chemotherapy. A DLT was defined as the occurrence of any of the following: (a) grade 4 hematologic toxicity, (b) febrile neutropenia, (c) any non-hematologic toxicity grade 3–4, and (d) any adverse event causing delay of treatment on days 15 and/or 28. The DLT level was reached when at least 50% of the patients treated at that dose level developed a DLT (i.e. at least two of three or three of six patients). The dose level of the maximum tolerated doses (MTDs), which will be the doses recommended for further phase II/III trial, was defined as the first level below the DLT dose level.

### Statistical considerations

The duration of response was measured from the first documentation of response until disease progression. The TTP was the interval between the initiation of treatment and the date when disease progression was first documented. Survival was measured from the date of registration to the study until the date of death. The follow-up time was measured from the day of registration to the study until the last contact or death. Data were analyzed with descriptive statistics using SPSS version 13.0 (SPSS Inc., Chicago, IL).

### Pharmacokinetic methods

Blood samples were collected at 0, 1, 3, 4, 6 and 10 h from the beginning of paclitaxel infusion, at 0 h (3 h after the beginning of paclitaxel infusion), 0.5, 1, 2, 6 and 9 h after gemcitabine infusion, and at 0 h (1.25 h after the beginning of gemcitabine infusion), 2, 6, and 8 h from the beginning of the oxaliplatin infusion. All blood samples were collected into heparinized tubes, placed on ice, and centrifuged at 1,500 rpm and 4°C for 10 min to separate the plasma from the blood cells. All samples were stored in three different aliquots at −80°C until analysis.

Paclitaxel measurements were based on a method described by Sparreboom et al. [21]. According to that, 100 µl of internal standard (docetaxel) and 5 ml of acetonitrile:*n*-butylchloride (1:4, v/v) were added to 1 ml of human plasma. The organic layer was evaporated to dryness under a stream of nitrogen at 60°C followed by reconstitution in 125 µl of methanol:water (1:1, v/v) and ultrasonication for 1 min. 100 µl of the solution was injected to HPLC system. The chromatographic analysis was achieved in an Inertsil ODS-80A column (150 × 4.6 mm, 5 µm; GL Science Inc., Tokyo, Japan) at 60°C and monitored at 230 nm with an ultraviolent detector. Mobile phase consisted of water:methanol:tetrahydrofuran:ammonium hydroxide (37.5:60:2.5:0.1, v/v) and adjusted to pH 6.0 with formic acid. Calibration curve was prepared in blank human plasma with standard concentrations of paclitaxel over the range of 0.01–2.0 µg/ml ($r^2 \geq 0.9993$). The lower limit of quantitation (LOQ) was determined at 0.01 µg/ml.

A previously described, HPLC method [8] was used to measure gemcitabine plasma samples. Analysis of gemcitabine samples was based on a reversed-phase column µ-Bondapack C18, (300 × 3.9 mm, 10 µm Waters, Milford, MA, USA) and monitored at 267 nm with ultraviolent detector. Standard calibration curve was over the range of 0.1–10 µg/ml ($r^2 \geq 0.9998$) and the LOQ was set at 0.078 µg/ml of plasma. Gemcitabine and paclitaxel were assayed on a LC-10A/10Avp Shimadzu chromatographic system (Shimadzu Deutchland GmbH, Duisburg, Germany) equipped with an SPD-M10Avp ultraviolet detector.

All oxaliplatin plasma samples were centrifuged at 2,000×*g* for 30 min at 4°C using Centricon (Ultracel YM-30) centrifuge filter devices of 30,000 Da cut-off (Millipore Co., Bedford, MA, USA). The ultra-filtrated fraction (free fraction) was used to measure the unbound to proteins oxaliplatin. Both total and ultra-filtrated samples were further diluted with 0.25% Triton X-100 (Fluka, Buchs SG, Switzerland). Oxaliplatin levels were determined by flameless atomic absorption spectrophotometry (FAAS) with deuterium correction on a Schimadzu system of an AA-6800 spectrophotometer (Schimadzu Deutchland GmbH, Duisburg, Germany) and a GFA-EX 7 graphite furnace at 265.9 nm [8, 22]. A typical standard calibration curve was over the range of 10–100 µg/l ($r^2 \geq 0.9998$). The LOQ was determined at 10 µg/l.

Pharmacokinetic parameters for paclitaxel, gemcitabine and free fraction of platinum were estimated using a

non-compartmental analysis by WinNonlin (Standard Edition version 2.1) program (Pharsight Co., Palo Alto, USA).

## Results

### Patients' characteristics

From January 2004 to December 2006, 27 patients with advanced solid tumors were enrolled in the study. The median age was 65 years (range 43–75), nine (33.3%) of the patients had PS 0, while 18 (66.7%) had PS 1. Further patients' demographics and clinical characteristics are presented in Table 1.

**Table 1** Patients' characteristics

| | No. of patients | % |
|---|---|---|
| Number of patients enrolled | 27 | |
| Age | | |
| Median (range) | 65 (43–75) | |
| Sex | | |
| Male | 13 | 48.1 |
| Female | 14 | 51.9 |
| Performance status (WHO) | | |
| 0 | 9 | 33.3 |
| 1 | 18 | 66.7 |
| Primary tumor | | |
| Non-small cell lung cancer | 5 | 18.5 |
| Bile duct | 5 | 18.5 |
| Breast | 3 | 11.1 |
| Urothelial | 3 | 11.1 |
| Unknown primary | 2 | 7.4 |
| Kidney | 2 | 7.4 |
| Mesothelioma | 2 | 7.4 |
| Ovaries | 1 | 3.7 |
| Melanoma | 1 | 3.7 |
| Endometrium | 1 | 3.7 |
| Non-Hodgkin lymphoma | 1 | 3.7 |
| Pancreas | 1 | 3.7 |
| Prior chemotherapy regimens | | |
| 0 | 11 | 40.7 |
| 1 | 6 | 22.2 |
| ≥2 | 10 | 37.1 |

### Dose-limiting toxicities

Table 2 shows the dose escalation levels, the number of patients enrolled at each dose level and the dose-limiting events observed during the first chemotherapy cycle. Grade 4 neutropenia was the most common DLT occurring in four patients and grade 3 febrile neutropenia in another one. The DLT dose level was reached at paclitaxel 110 mg/m$^2$, gemcitabine 1,150 mg/m$^2$ and LOHP 70 mg/m$^2$ since two out of three patients developed DLT events. Therefore, the recommended doses for future phase II studies are paclitaxel 110 mg/m$^2$, gemcitabine 1,000 mg/m$^2$ and LOHP 70 mg/m$^2$ on days 1 and 15 in 28 days cycles.

### Compliance with treatment

A total of 109 chemotherapy cycles were administered with a median of 3 cycles/patient. The median interval between cycles was 30 days (range 28–45). Treatment was discontinued due to disease progression ($n = 18$ patients), treatment refusal ($n = 1$ patient), completion of treatment ($n = 6$ patients) and toxicity ($n = 2$ patients, one with grade 3 neurotoxicity and one with grade 3 mucositis). Dose reduction was required in 25 (23%) cycles, for hematologic toxicity ($n = 10$ cycles), non-hematologic toxicity ($n = 14$ cycles) or both ($n = 1$ cycle). Treatment delay was observed in 35 (32.1%) cycles due to hematologic ($n = 3$ cycles), non-hematologic ($n = 2$ cycle) toxicity or other reasons not related to disease or treatment ($n = 30$ cycles), i.e. late admission or pending imaging studies for response evaluation. The median time of treatment delay was 9 days (range 4–58).

### Hematological and non-hematological toxicity

All patients were evaluable for toxicity. Table 3 demonstrates the worst toxicity per patient in all cycles. Tables 4 and 5 demonstrate the hematologic and non-hematologic toxicity in all cycles by dose level. Neutropenia was the most common adverse event of the combination. Grade 2 and 3 neutropenia was observed in three (11.1%) and six (22.2%) patients, respectively, whereas, grade 4 neutropenia was observed in four (14.8%) patients. Three episodes of febrile neutropenia were observed, two in the 4th and one in the 5th dose level and all required hospitalization for intravenous antibiotics. Grade 3 anemia and thrombocytopenia occurred in one patient each, whereas grade 4 anemia was observed in another patient. Non-hematologic toxicity was generally mild. Fatigue was a common complaint among patients reaching grade 2 in ten (37%) and grade 3 in three (11.1%) patients. Grade 2 and 3 neurotoxicity was observed in one (3.7%) and two (7.4%) patients, respectively, and one (3.7%) patient presented with grade 4 neurotoxicity. In addition, grade 3 and 4 nausea/vomiting

**Table 2** Dose escalation levels, number of patients enrolled, and dose-limiting toxicities

| Level | Paclitaxel ($mg/m^2$) (d1 and d15) | Gemcitabine ($mg/m^2$) (d1 and d15) | Oxaliplatin ($mg/m^2$) (d1 and d15) | No. of patients | DLT (no. of patients) |
|---|---|---|---|---|---|
| 1 | 100 | 800 | 50 | 3 | – |
| 2 | 100 | 800 | 60 | 3 | – |
| 3 | 100 | 1,000 | 60 | 6 | Grade 4 neutropenia ($n = 1$) |
| 4 | 110 | 1,000 | 60 | 6 | Grade 3 febrile neutropenia ($n = 1$) |
| 5 | 110 | 1,000 | 70 | 6 | Grade 4 neutropenia ($n = 1$) |
| 6 | 110 | 1,150 | 70 | 3 | Grade 4 neutropenia ($n = 2$) |

**Table 3** Worst toxicity per patient in all cycles of the paclitaxel/gemcitabine/lohp combination ($n$ = number of patients)

| | Toxicity grade | | | | | |
|---|---|---|---|---|---|---|
| | 2 | | 3 | | 4 | |
| | *n* | % | *n* | % | *n* | % |
| Neutropenia | 3 | 11.1 | 6 | 22.2 | 4 | 14.8 |
| Anemia | 8 | 29.6 | 1 | 3.7 | 1 | 3.7 |
| Thrombocytopenia | 3 | 11.1 | 1 | 3.7 | – | – |
| Febrile neutropenia | – | – | 2 | 7.4 | 1 | 3.7 |
| Fatigue | 10 | 37 | 3 | 11.1 | – | – |
| Nausea/vomiting | 1 | 3.7 | 4 | 14.8 | 1 | 14.8 |
| Neurotoxicity | 1 | 3.7 | 2 | 7.4 | 1 | 3.7 |
| Hypersensitivity reactions | 1 | 3.7 | – | – | – | – |
| Mucositis | – | – | 1 | 3.7 | – | – |

was observed in four (14.8%) and one (3.7%) patients, respectively. There was no treatment-related death.

## Efficacy

Twenty-four of the 27 patients had measurable disease and received at least 2 cycles of chemotherapy and, therefore, were evaluable for response. One complete response (CR) was observed in a patient with ovarian cancer. Partial response (PR) was achieved in five patients (one with urothelial cancer, one with cancer of unknown primary, one with non-small cell lung cancer and two with mesothelioma). Three responses were observed in chemotherapy-naïve patients or in patients who had received only one prior chemotherapy regimen and another three in more heavily pretreated patients. Responses were observed in all dose levels studied. Stable disease (SD) was noted in 4 patients and progressive disease (PD) in 17. The median response duration was 2.6 months (range 2–4.2). The median TTP for the whole group of patients was 3.1 months (range 1.5–21) and for the patients who had clinical benefit (i.e. those with CR, PR or SD) 7 months (range 5.5–21).

## Pharmacokinetics

Sampling was performed in 13 patients during the first treatment, and the effects of dose escalation on the PK parameters of the combination are shown in Table 6. The pharmacokinetics of paclitaxel were characterized by $C_{max}$ ranging from 0.50 to 1.61 mg/l, with a post-infusional elimination half-life mean value of 4.5 h, and AUC for all time points ($AUC_{all}$) between 3.06 and 7.63 mg h/l. Pharmacokinetics of gemcitabine were defined by $C_{max}$ varying from 4.3 to 22.3 mg/l, detected at the end of the drug infusion ($t_{max}$ 0.5 h), and by an elimination with $t_{1/2}$ and CL mean values of 0.43 h and 102.3 l/h, respectively (Table 6). The analysis of ultra-filtrated plasma fraction produced a PK profile for LOHP with $C_{max}$, $t_{1/2}$, $AUC_{all}$ and CL mean values of 0.10 mg/l, 14.9 h, 1.42 mg h/l and 0.041 l/h, respectively.

**Table 4** Hematologic toxicity (NCI-CTC grades 2–4) in all cycles by dose level

| Dose level | No. of cycles | Neutropenia | | | Anemia | | | Thrombocytopenia | | | Febrile neutropenia | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 |
| 1 | 12 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 13 | 2 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 18 | 0 | 1 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 36 | 3 | 5 | 0 | 5 | 0 | 0 | 4 | 0 | 0 | 0 | 2 | 0 |
| 5 | 20 | 0 | 1 | 2 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| 6 | 10 | 1 | 0 | 2 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Overall (%) | 109 | 7 (6.5) | 7 (6.5) | 5 (4.6) | 14 (13) | 1 (0.9) | 1 (0.9) | 4 (3.7) | 1 (0.9) | 0 (0) | 0 (0) | 2 (1.8) | 1 (0.9) |

**Table 5** Non-hematologic toxicity (NCI-CTC grades 2–4) in all cycles by dose level

| Dose level | No. of cycles | Nausea/vomiting | | | Neurotoxicity | | | Fatigue | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | G2 | G3 | G4 | G2 | G3 | G4 | G2 | G3 | G4 |
| 1 | 12 | 1 | 2 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| 2 | 13 | 3 | 1 | 0 | 1 | 0 | 2 | 7 | 0 | 0 |
| 3 | 18 | 3 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| 4 | 36 | 0 | 0 | 0 | 2 | 4 | 0 | 3 | 3 | 0 |
| 5 | 20 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 |
| 6 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Overall (%) | 109 | 7 (6.5) | 3 (2.7) | 0 (0) | 3 (2.7) | 4 (3.7) | 2 (1.8) | 18 (16.5) | 5 (4.6) | 0 (0) |

**Table 6** Major pharmacokinetic parameters of the combination at the different dose levels

| Dose levels (no. of patients) | 1 (3) | 2 (2) | 3 (2) | 4 (2) | 5 (2) | 6 (2) |
|---|---|---|---|---|---|---|
| Paclitaxel | | | | | | |
| $C_{max}$ | 0.89 (0.38) | 1.28 (0.06) | 1.12 (0.31) | 0.95 (0.29) | 1.23 (0.38) | 1.09 (0.01) |
| $t_{1/2}$ | 5.6 (3.1) | 3.5 (1.7) | 5.6 (0.7) | 4.4 (2.2) | 6.1 (0.1) | 1.6 (0.1) |
| $AUC_{all}$ | 4.29 (0.19) | 4.94 (0.19) | 6.77 (0.85) | 4.70 (1.64) | 5.80 (1.62) | 3.57 (0.15) |
| $Cl_{(observed)}$ | 0.021 (0.001) | 0.021 (0.002) | 0.014 (0.001) | 0.027 (0.012) | 0.019 (0.005) | 0.032 (0.001) |
| $Vz_{(observed)}$ | 0.17 (0.09) | 0.10 (0.04) | 0.12 (0.03) | 0.13 (0.01) | 0.16 (0.04) | 0.07 (0.0) |
| Gemcitabine | | | | | | |
| $C_{max}$ | 9.5 (2.1) | 9.3 (3.5) | 7.0 (2.6) | 9.7 (1.6) | 15.8 (6.5) | 13.5 (2.4) |
| $t_{1/2}$ | 0.43 (0.11) | 0.44 (0.10) | 0.62 (0.05) | 0.45 (0.03) | 0.36 (0.01) | 0.28 (0.03) |
| $AUC_{all}$ | 11.7 (6.0) | 10.4 (2.7) | 11.0 (5.2) | 10.2 (0.5) | 13.1 (4.4) | 9.7 (0.7) |
| $Cl_{(observed)}$ | 88.0 (38.5) | 80.9 (17.5) | 138.0 (67.7) | 99.3 (1.0) | 91.7 (28.9) | 123.0 (9.1) |
| $Vz_{(observed)}$ | 51.1 (18.1) | 54.2 (22.5) | 127.9 (70.6) | 64.2 (3.8) | 48.8 (17.0) | 49.9 (9.1) |
| LOHP | | | | | | |
| $C_{max}$ | 80.9 (25.6) | 108.5 (8.9) | ND | 105.9 (28.7) | 127.1 (32.4) | 89.9 (4.8) |
| $t_{1/2}$ | 11.1 (3.5) | 5.1 (0.0) | ND | 16.3 (1.7) | 23.9 (14.8) | 20.3 (6.7) |
| $AUC_{all}$ | 1.03 (0.47) | 1.38 (0.21) | ND | 1.53 (0.67) | 2.07 (0.69) | 1.26 (0.12) |
| $Cl_{(observed)}$ | 0.06 (0.05) | 0.04 (0.01) | ND | 0.03 (0.01) | 0.03 (0.02) | 0.04 (0.07) |
| $Vz_{(observed)}$ | 0.74 (0.27) | 0.31 (0.05) | ND | 0.69 (0.24) | 0.55 (0.03) | 0.89 (0.07) |

*ND* not determined, *LOHP* oxaliplatin (ultra-filtrated free fraction)

## Discussion

The present study demonstrates that the biweekly administration of the paclitaxel, gemcitabine and LOHP combination in patients with advanced solid tumors is feasible and generally well tolerated. Severe neutropenia and febrile neutropenia were the most common toxicities leading in dose-limiting adverse events. The MTD of the combination was paclitaxel 110 mg/m$^2$, gemcitabine 1,000 mg/m$^2$ and LOHP 70 mg/m$^2$ and on days 1 and 15 in cycles every 4 weeks.

The same combination but with different doses and schedule (paclitaxel 80 mg/m$^2$ and gemcitabine 800 mg/m$^2$ on days 1 and 8 and LOHP 130 mg/m$^2$ on day 1 in 3-week cycle) has been administered in a phase II study to 41 patients with cisplatin refractory or multiply relapsed germ-cell tumors [23]. In this heavily pretreated patient population, 5% CRs and 46% PRs were achieved and the main toxicities were grade 3 and 4 leucocytopenia in 15%, grade 3 and 4 anemia in 7% and grade 3 and 4 thrombocytopenia in 49% of the patients. Interestingly, no excess neurotoxicity (2%) was observed despite the combination of two potentially neurotoxic drugs [23]. Although the two trials are not comparable, in the current study grade 3 and 4 neutropenia occurred in 22% and 15% of patients, respectively, and grade 3 and 4 ane-

mia and thrombocytopenia were mild occurring in 7.4% and 3.4% of the patients, respectively. Non-hematologic toxicity was generally mild and the incidence of neurotoxicity was relatively low, since grade 2 and 3 was observed in 11.1% and grade 4 in 3.7% of the patients. The good tolerance of the regimen is especially important in view of the characteristics of the study population (median age 65 years; 37.1% of patients heavily pretreated having received at least two prior chemotherapy regimens).

In contrast, in another small study from Italy, with the same drug combination given weekly (paclitaxel 70 mg/m$^2$, LOHP 50 mg/m$^2$ and gemcitabine 800 mg/m$^2$ on days 1, 8 and 15 in cycles of 4 weeks) in nine cisplatin refractory germ-cell tumor patients the results were not as promising [24]. The authors concluded that the combination was not feasible in that heavily pretreated patient population due to excessive hematological toxicity, in particular severe thrombocytopenia (only one patient could continue the schedule) [24].

Furthermore, several other groups have studied different two-drug combinations of the above-mentioned agents for possible PK interactions [25–28]. Nevertheless, the present study aimed to examine, for the first time, possible PK interactions between all three drugs of the combination. The PK analysis in our study demonstrated absence of any correlation between major PK parameters of combined drugs. The present combination of three agents did not significantly affect the pharmacokinetics of individual drugs. Although nonproportional to the escalated doses, all studied parameters were found to be in accordance with other published reports [6, 8].

Although response to treatment was not a primary endpoint of this phase I trial, CR was observed in one patient with ovarian cancer and partial response in five patients with various types of tumors. In addition, responses were observed in malignancies other than genitourinary, suggesting that the combination merits further evaluation in other types of tumors as well. Three responses were observed in chemotherapy-naïve patients or after only one prior chemotherapy regimen and another three in more heavily pretreated patients. Thus, this combination can be considered active in pretreated patients with solid tumors.

In conclusion, the results of the present phase I study indicate that the biweekly combination of paclitaxel, gemcitabine and LOHP is feasible and with an acceptable toxicity profile. This regimen shows promising activity in different types of solid tumors and merits further evaluation as front-line or salvage treatment in patients with advanced cancer such as gynecologic, genitourinary malignancies and mesotheliomas.

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## References

1. Hamilton A, Hortobagyi G (2005) Chemotherapy: what progress in the last 5 years? J Clin Oncol 23:1760–1775
2. Rigas JR (2004) Taxane–platinum combinations in advanced non-small cell lung cancer: a review. Oncologist 9:16–23
3. Poveda A (2005) Ovarian cancer: is the news good enough? Int J Gynecol Cancer 15:298–306
4. Kouroussis C, Kakolyris S, Mavroudis D et al (2001) A dose-finding study of the weekly administration of paclitaxel in patients with advanced solid tumors. Am J Clin Oncol 24:404–407
5. Green MC, Buzdar AU, Smith T et al (2005) Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. J Clin Oncol 23:5983–5992
6. Kalbakis K, Pappas P, Kouroussis C et al (2008) A dose escalation and pharmacokinetic study of biweekly pegylated liposomal doxorubicin, paclitaxel and oxaliplatin in patients with advanced solid tumors. Cancer Chemother Pharmacol 62:449–456
7. Chitkovic E (1998) Ongoing and unsaid on oxaliplatin: the hope. Br J Cancer 77:8–11
8. Mavroudis D, Pappas P, Kouroussis C et al (2003) A dose-escalation and pharmacokinetic study of gemcitabine and oxaliplatin in patients with advanced solid tumors. Ann Oncol 14:304–312
9. Louvet C, Andre T, Tigaud JM et al (2002) Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol 20:4543–4548
10. Bible KC, Boerner SA, Kirkland K et al (2000) Characterization of an ovarian carcinoma cell line resistant to cisplatin and flavopiridol. Clin Cancer Res 6:661–670
11. Souglakos J, Kakolyris S, Vardakis N et al (2005) A dose escalating study of oxaliplatin and high dose weekly leucovorin and 5-fluorouracil in patients with advanced solid tumors. Cancer Invest 23:505–510
12. Fujie Y, Yamamoto H, Ngan CY et al (2005) Oxaliplatin, a potent inhibitor of surviving, enhances paclitaxel induced apoptosis and mitotic catastrophe in colon cancer cells. Jpn J Clin Oncol 35:453–463
13. Faivre S, Kalla S, Cvitkovic E et al (1999) Oxaliplatin and paclitaxel combination in patients with platinum-pretreated ovarian carcinoma: an investigator-originated compassionate-use experience. Ann Oncol 10:1125–1128
14. Harnett P, Buck M, Beale P et al (2007) Phase II study of gemcitabine and oxaliplatin in patients with recurrent ovarian cancer: an Australian and New Zealand Gynaecological Oncology Group study. Int J Gynecol Cancer 17:359–366
15. Silver DF, Piver MS (1999) Gemcitabine salvage chemotherapy for patients with gynecologic malignancies of the ovary, fallopian tube, and peritoneum. Am J Clin Oncol 22:450–452
16. Faivre S, Raymond E, Rixe O (1998) Preclinical synergy of oxaliplatin in combination with other antitumor agents. Ann Oncol 9:131 (Abstract 627P)
17. Germano D, Rosati G, Manzione L (2007) Gemcitabine combined with oxaliplatin (GEMOX) as salvage treatment in elderly patients with advanced ovarian cancer refractory or resistant to platinum: a single institution experience. J Chemother 19:577–581
18. Yang X, Cai Y, Zhao X et al (2008) Biweekly docetaxel-containing chemotherapy may be the optimal schedule. Anticancer Drugs 19:421–426
19. Therasse P, Arbuck SG, Eishenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumor. JNCI 92:205–216

20. National Cancer Institute (2003) Common Toxicity Criteria version 3.0. http://ctep.cancer.gov/reporting/ctc.html
21. Sparreboom A, de Bruijn P, Nooter K et al (1998) Determination of paclitaxel in human plasma using single solvent extraction prior to isocratic reversed-phase high-performance liquid chromatography with ultraviolet detection. J Chromatogr B Biomed Sci Appl 705:159–164
22. Wasserman E, Cuvier C, Lokiec F et al (1999) Combination of oxaliplatin plus irinotecan in patients with gastrointestinal tumors: results of two independent phase I studies with pharmacokinetics. J Clin Oncol 17:1751–1759
23. Bokemeyer C, Oechsle K, Honecker F et al (2008) Combination chemotherapy with gemcitabine, oxaliplatin and paclitaxel in patients with cisplatin-refractory or multiply relapsed germ-cell tumors: a study of the German Testicular Cancer Study Group. Ann Oncol 19:448–453
24. De Giorgi U, Rosti G, Papiani G et al (2004) Weekly gemcitabine, paclitaxel, oxaliplatin combination chemotherapy in patients with cisplatin-refractory germ cell tumors. Preliminary experience. Am J Clin Oncol 27:457–460
25. Fogli S, Danesi R, DeBraud F et al (2001) Drug distribution and pharmacokinetic/pharmacodynamic relationship of paclitaxel and gemcitabine in patients with non-small-cell lung cancer. Ann Oncol 12:1553–1559
26. Gan HK, Mitchell PL, Galettis P et al (2006) A phase 1 and pharmacokinetic study of gemcitabine and oxaliplatin in patients with solid tumors. Cancer Chemother Pharmacol 58:157–164
27. Liu J, Kraut E, Bender J et al (2002) Pharmacokinetics of oxaliplatin (NSC 266046) alone and in combination with paclitaxel in cancer patients. Cancer Chemother Phar macol 49:367–374
28. Kroep JR, Giaccone G, Voorn DA et al (1999) Gemcitabine and paclitaxel: pharmacokinetic and pharmacodynamic interactions in patients with non-small-cell lung cancer. J Clin Oncol 17:2190–2197