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ORIGINAL ARTICLE

Pharmacokinetic evaluation of platinum derived from cisplatin administered alone and with pemetrexed in head and neck cancer patients

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Abstract
Purpose This phase I study characterized the pharmacokinetics of free and total platinum derived from cisplatin administered alone and in combination with pemetrexed. Secondary objectives were to assess the pharmacokinetics of pemetrexed when it is combined with cisplatin as well as to evaluate the safety profile and document antitumor activity associated with this combination.
Methods An open-label, two-arm, cross-over phase 1 study was performed in patients with squamous cell carcinoma of the head and neck, age $\geq$18 years, an Eastern Cooperative Oncology Group performance status of 0–2, and adequate organ function. Blood samples were taken and pharmacokinetics evaluated for the first two cycles using noncompartmental analysis. Patients received either pemetrexed (500 mg m^{-2}) plus cisplatin (75 mg m^{-2}) administered in cycle 1 followed by cisplatin alone in cycle 2; or in the reverse order (i.e., cisplatin alone in cycle 1 followed by pemetrexed plus cisplatin in cycle 2). Each treatment cycle was 21 days and patients received folic acid, vitamin B_{12} supplementation, and dexamethasone prophylaxis. After the first two cycles, patients continued study treatment with pemetrexed plus cisplatin every 3 weeks up to a maximum of six total treatment cycles. Toxicities were graded by the investigators according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0.
Results A total of 13 patients were treated; one patient was discontinued from the study after cycle 1 for failure to meet baseline eligibility criteria for renal function. The ratios and 90% confidence intervals (CI) comparing the pharmacokinetics for cisplatin administered with pemetrexed to those for cisplatin administered alone for free platinum were: C_{max} = 1.08 (CI: 0.92, 1.27) and AUC = 0.93 (CI: 0.82, 1.06); and, total platinum were: C_{max} = 0.97 (CI: 0.88, 1.06) and AUC = 0.87 (CI: 0.81, 0.93). These results indicate that platinum pharmacokinetics (free and total) are similar, whether cisplatin is administered alone or combined with pemetrexed. The pemetrexed pharmacokinetic results were consistent with those from previous single-agent pemetrexed studies and a previous study of pemetrexed in combination with cisplatin. The combination of pemetrexed and cisplatin did not show any unexpected toxicities. Consistent with the platinum pharmacokinetic results, co-administration with pemetrexed did not appear to enhance cisplatin-related toxicities. Of the 13 treated patients, 11 had stable disease as the best overall response and 2 had progressive disease.
Conclusions The pharmacokinetics of free platinum derived from cisplatin were not altered by co-administration with pemetrexed, and in agreement with this, no unexpected cisplatin-induced toxicities were observed when these drugs were combined.

Keywords Pemetrexed · Cisplatin · Platinum · Pharmacokinetics · Head and neck cancer

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Introduction

Pemetrexed, a novel antimetabolite, acts as a multitargeted antifolate by inhibiting several key enzymes involved in nucleotide synthesis [1]. In clinical studies, antitumor activity has been observed in a wide variety of solid tumors, including malignant pleural mesothelioma (MPM), breast, colorectal, pancreatic, gastric, bladder, cervix, lung and head and neck cancer [2]. Pemetrexed is approved for use in combination with cisplatin for the treatment of chemotherapy-naive patients with MPM, and as a single agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy [3, 4]. The European Medicines Agency (EMEA) recently approved pemetrexed in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC [5].

The pharmacokinetics of total platinum and pemetrexed were previously evaluated in patients with MPM using population pharmacokinetic methods and there was no significant influence of concomitant cisplatin administration on pemetrexed clearance or of concomitant pemetrexed administration on cisplatin clearance [6]. For the purposes of a cross-over study design most appropriate to determine whether there is an alteration in free platinum pharmacokinetics after administration of cisplatin alone and in combination with pemetrexed, it was no longer feasible to administer cisplatin alone to patients with MPM for ethical reasons; therefore, an appropriate patient population was sought for this trial that would be eligible to receive treatment with either single-agent cisplatin or platinum doublet chemotherapy.

Cisplatin monotherapy is a standard of care in patients with advanced head and neck cancer (HNC) [7]. Single-agent pemetrexed has shown promising activity in patients with locally advanced or metastatic HNC [8]. In a phase 1 study conducted in approximately 12 patients with advanced solid tumors, 3 patients with HNC had partial responses to combined treatment with cisplatin and pemetrexed [9]. An ongoing phase III study is evaluating pemetrexed in combination with cisplatin versus cisplatin alone in patients with recurrent/metastatic head and neck cancer [10]. Therefore, the HNC population with locoregional recurrence or metastatic disease was identified for this study.

Both cisplatin and pemetrexed are predominantly eliminated renally and both are protein bound; pemetrexed is approximately 80% protein-bound and cisplatin-derived platinum is >90% protein-bound [6, 11]. Because the free (unbound) platinum fraction derived from cisplatin is low, a small absolute alteration in free platinum concentration may translate into a large relative alteration in this free fraction. A significant increase in the unbound platinum fraction has the potential to increase toxicity, whereas a significant decrease in free platinum exposure has the potential to negatively impact efficacy outcome. Thus, the primary objective of this study was to determine whether there were any alterations in free platinum concentrations when cisplatin was administered with pemetrexed.

Materials and methods

Eligibility criteria

Patients with a confirmed histologic or cytologic diagnosis of squamous cell HNC, with either locoregional disease recurrence or metastatic disease, were eligible for enrollment in this study. Patients with locoregional recurrence could not be candidates for curative surgical or radiation therapy, and prior therapy (surgery, radiation and/or 1 prior course of chemotherapy) had to be completed at least 60 days before study enrollment. Other eligibility criteria included, age $\geq$18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, estimated life expectancy $\geq$3 months, calculated creatinine clearance $\geq$60 mL min^{-1}, absolute neutrophil count $\geq 1.5 \times 10^9$ L^{-1}, platelet count $\geq 100 \times 10^9$ L^{-1}, hemoglobin $\geq$9 g dL^{-1}, bilirubin $\leq$1.5 times the upper limit of normal, and hepatic transaminases $\leq$3 times the upper limit of normal or <5 times upper limit of normal if due to metastatic liver disease.

Patients were excluded from study participation for symptomatic or active brain metastases, clinically significant pleural or peritoneal effusions, inability to take vitamin supplementation or prophylactic corticosteroids, inability to interrupt nonsteroidal anti-inflammatory therapy, or a second primary malignancy that was clinically detectable at the time of consideration for study enrollment.

This study was conducted according to the principles of good clinical practices, applicable local laws and regulations, and the Declaration of Helsinki. The protocol was approved by the respective institutional review boards at participating sites, and all patients provided written informed consent before treatment.

Study design and treatment

This phase I trial was an open-label, two-arm, cross-over design study performed in patients with squamous cell HNC, with pharmacokinetic sampling conducted during the first two treatment cycles. One group of patients received pemetrexed and cisplatin during cycle 1, followed by cisplatin alone during cycle 2 (treatment arm A). The other group received cisplatin alone during cycle 1, followed by pemetrexed and cisplatin during cycle 2 (treatment arm B).

Each treatment cycle lasted 21 days. Patients received the pemetrexed–cisplatin combination for the remaining cycles. In the absence of unacceptable toxicities or disease progression, patients were permitted to receive up to a maximum of six total treatment cycles.

For the single-agent cisplatin treatment cycle, cisplatin 75 mg m^{-2} was administered by intravenous (IV) mode over approximately 120 min. For the pemetrexed plus cisplatin treatment cycles, pemetrexed 500 mg m^{-2} was administered IV over approximately 10 min followed by cisplatin over approximately 120 min, starting approximately 30 min after the pemetrexed infusion was completed. Both agents were administered on day 1 of the 21-day treatment cycle.

To reduce the incidence and severity of skin reactions, all patients began treatment with oral dexamethasone (4 mg twice daily) the day before pemetrexed cycles began and continued through the day after the 21-day cycle ended. All patients received vitamin supplementation, which included a vitamin B_{12} injection (1,000 μg) 1–2 weeks before day 1 and every 9 weeks during study entry and folic acid (350–1,000 μg) 1–2 weeks before day 1, continuing daily. Supplementation continued until 3 weeks after the last dose of pemetrexed and cisplatin.

Drug doses were modified in the event of unacceptable hematologic (absolute neutrophil count of $<1.5 \times 10^9$ L^{-1} or platelets $<100 \times 10^9$ L^{-1}) or nonhematologic toxicities such as grade 3 or 4 diarrhea, grade 3 or 4 mucositis, grade 2 neuropathy, or other selected toxicities. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale, version 3.0 [12]. Study therapy was delayed for up to 42 days in patients who developed renal impairment, defined by a calculated creatinine clearance <60 mL min^{-1}. All patients who required a dose reduction received a reduced dose for the remainder of the study. Patients were discontinued from study treatment in the event of grade 3/4 neurosensory toxicity, any recurrent toxicity that would require a third dose reduction, or other unacceptable toxicity.

Baseline and treatment assessments

Medical histories, physical examinations, hematologic and blood chemistry assessments, and evaluation of ECOG performance status were obtained at baseline and before each cycle of treatment. Laboratory studies were performed weekly while patients were on study. Creatinine clearance was calculated using the original weight-based Cockcroft–Gault method [13]. Adverse events were assessed using the CTCAE scale. Investigator assessment of tumor response was recorded.

Blood samples for pharmacokinetic analysis of pemetrexed, and total and free platinum were collected during cycles 1 and 2. Plasma samples for measurement of total platinum were collected up to approximately 504 h (21 days) after dose administration. The half-life of total platinum over the first 5 days after rapid infusions of cisplatin has been reported to vary from 4.2 to 7.2 days [14]; therefore, the sampling schedule allowed for complete characterization of total platinum pharmacokinetics. Plasma samples for measurement of free platinum were collected up to approximately 24 h after administration of cisplatin. Because the unbound fraction declines rapidly, this sampling scheme permitted adequate evaluation of free platinum kinetics [15].

Blood samples for platinum analysis were collected just before drug administration and at 0.5, 1, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 192, 360, and 528 h after drug administration. Samples for free platinum analysis were collected at the same intervals until 24 h after drug administration. Heparinized plasma samples were analyzed for free and total platinum derived from cisplatin using a validated inductively coupled plasma mass spectrometry method over the concentration range of 50–2000 ng mL^{-1} (CANTEST Ltd., North Vancouver, BC, Canada).

Blood samples for pemetrexed analysis were taken just before administration and at 10, 40, 70, 100, 160, 220, 280, 400, 520, and 760 min and 24 and 48 h after the start of infusion. Pemetrexed concentrations in heparinized plasma samples were measured using a high-performance liquid chromatography electrospray ionization tandem mass spectrometry method over the concentration range of 10–200,000 ng mL^{-1} [16]. Samples were analyzed for pemetrexed at Taylor Technology, Inc. (Princeton, NJ, USA).

Pharmacokinetic analyses

The pharmacokinetic parameters for free platinum, total platinum, and pemetrexed were computed by standard noncompartmental methods (WinNonlin Enterprise, Version 5.0.1, Pharsight Corp., Cary, NC). Pharmacokinetic parameters determined based on plasma concentration versus time data were area under the plasma concentration (AUC) versus time curve from zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), elimination half-life ($t_{1/2}$), volume of distribution at steady-state (V_{ss}) and total systemic clearance (CL).

Statistical analyses

The influence of pemetrexed administration on the pharmacokinetic parameters of free and total platinum was evaluated using a mixed-effects model with patient as a random effect and treatment regimen (pemetrexed plus cisplatin and cisplatin alone), period, and sequence, as fixed effects. Least squares geometric means, ratios of the least squares

geometric means for the two treatments, and 90% confidence intervals (CI) were estimated for $AUC_{0-\infty}$ and C_{max}. All pharmacokinetic parameters were logarithmically transformed before analysis.

All patients who received at least one dose of cisplatin or pemetrexed were evaluated for safety. Safety analyses included summaries of the extent of exposure, the number of blood transfusions needed, adverse events (AEs), including deaths, serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs).

A formal efficacy analysis was not conducted for this phase 1 trial. Investigators assessed tumor response and the investigator-reported results were summarized.

Results

Patient characteristics and disposition

The study was conducted at two sites, one in Belgium and one in Romania, from 13 September 2006 to 8 May 2007; 13 patients were enrolled. Table 1 summarizes the demographic data for all patients. Eight (61.5%) of the 13 patients (4 patients in each treatment arm) had received prior systemic therapy. Cisplatin was the most frequently given systemic therapy, followed by 5-fluorouracil. Ten (76.9%) patients (5 in each treatment arm) had received prior locoregional radiotherapy. Seven (53.8%) patients (i.e., 3 in treatment arm A and 4 in treatment arm B) had undergone prior locoregional surgical resection.

Table 1 Summary of patient demographics and baseline characteristics

Characteristic	Patients ($N = 13$)
Age (years)	
Median	56
Range (minimum–maximum)	36–74
Sex	
Male (*n*) (%)	11 (84.6%)
Origin	
Caucasian (*n*) (%)	13 (100%)
Had a locoregional disease stage (*n*) (%)	7 (53.8%)
Had a local disease stage (*n*) (%)	5 (38.5%)
Had a metastatic disease stage (*n*) (%)	1 (0.08%)
Received prior systemic therapy (*n*) (%)	8 (61.5%)
Received prior radiotherapy (*n*) (%)	10 (76.9%)
Received prior surgery (*n*) (%)	7 (53.8%)
Performance status	
ECOG PS 0 (*n*) (%)	1 (7.7%)
ECOG PS 1 (*n*) (%)	11 (84.6%)
ECOG PS 2 (*n*) (%)	1 (7.7%)

Abbreviations: *ECOG* Eastern Cooperative Oncology Group, *PS* performance status

Thirteen patients received at least one dose of study drug, and three completed the maximum six cycles of study treatment. The most common reason for discontinuation was progressive disease, which occurred in 6 of the 13 patients (46.2%). No deaths occurred during study treatment. Two patients died from progressive disease within 30 days after study treatment ended, and these deaths were not considered related to study treatment.

One patient that was enrolled and assigned to treatment arm B was treated despite having a baseline creatinine clearance of 39.6 mL min^{-1}, less than the 60-mL min^{-1} protocol-specified minimum. This patient received the first cycle (cisplatin alone) and blood samplings were taken for pharmacokinetic analysis and the patient was removed from the study after the first treatment cycle. Although no longer formally participating in the study, this patient did receive five cycles of pemetrexed and cisplatin without complication.

Treatment

A total of 53 treatment cycles were administered (median, 4; range, 1–6). During the first two cycles of the study, there were no dose reductions and one patient had a dose delay because of logistic reasons. In the remaining cycles, seven patients had dose delays; three were because of logistic reasons and four were clinically indicated for low creatinine clearance, anemia, infection and mucositis. One patient required a dose reduction due to low platelets, anemia and mucositis.

Pharmacokinetics

Platinum plasma concentration data were evaluated for all 13 patients enrolled in the study. Individual free platinum plasma concentration time profiles were similar following treatment with cisplatin alone and cisplatin plus pemetrexed (Fig. 1a). Total and free platinum pharmacokinetics combining both treatment arms were consistent (Table 2). Total platinum plasma concentration time profiles were similar after administration of cisplatin alone compared with cisplatin plus pemetrexed in this study as well as similar to exposures observed in a separate cisplatin plus pemetrexed study (Fig. 1b) [17].

Table 3 presents the 90% confidence intervals for the overall comparison of platinum pharmacokinetics for cisplatin administered in combination with pemetrexed to cisplatin administered alone. The dose-normalized C_{max} and AUC for total platinum were both higher in cycle 2 than in cycle 1, whether cisplatin was administered alone or with pemetrexed in either treatment arm. These results reflect the

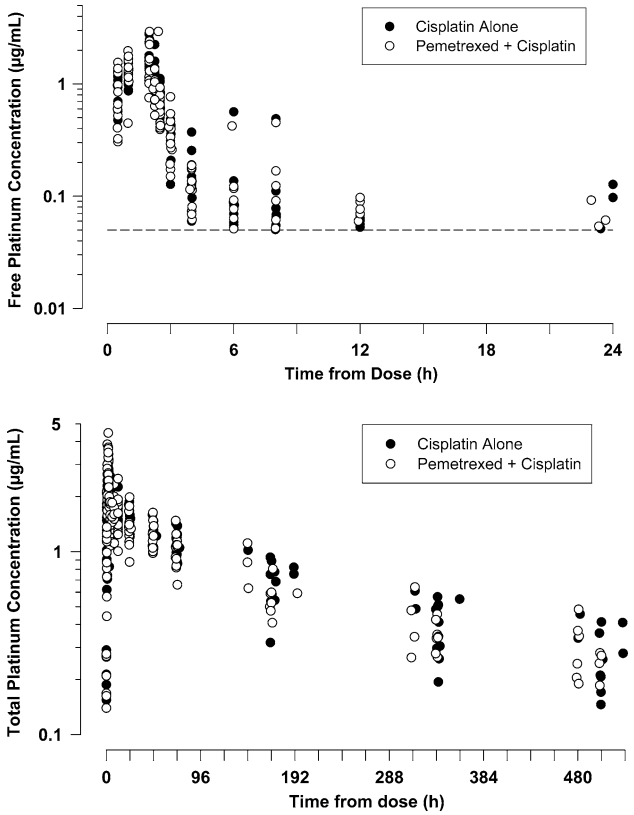

Fig. 1 Platinum concentration in plasma versus time for cisplatin alone versus pemetrexed plus cisplatin (*Panel* **a** Free platinum, *Panel* **b** total platinum)

sequence effect due to the long terminal elimination half-life of total platinum as seen from Table 2, half-life ranging up to 113 h or approximately 5 days. The two-arm cross-over design corrects for the potential bias of carry-over effect. Combining the two treatment arms, the ratio (and 90% CI) were 0.97 (0.88–1.06) for C_{max} and 0.87 (0.81–0.93) for AUC, indicating that total platinum pharmacokinetics are similar whether cisplatin was administered alone or with pemetrexed. The ratio (90% CIs) for the comparison of free platinum pharmacokinetics for cisplatin administered in combination with pemetrexed to those for cisplatin administered alone were: 1.08 (0.92–1.27) for C_{max}, and 0.93 (0.82–1.06) for AUC. As could be expected, there was no evidence of a carry-over effect for free platinum.

As previously mentioned, one patient was determined not to meet the baseline eligibility criteria relative to renal function after receiving one dose of single-agent cisplatin. Although the statistical analysis used takes such imbalance into account, because the pharmacokinetic data for this patient did not allow an intra-individual comparison, a second comparative analysis was conducted that excluded this patient's pharmacokinetic data altogether. That analysis yielded similar results to those provided above, and thus, did not change the pharmacokinetic conclusions.

Pemetrexed plasma concentration data were evaluated for the 12 patients for whom these data were available. The C_{max} occurred at the end of the infusion as expected, and the multiexponential decay in the pharmacokinetic profiles from patients in the current study were similar to those seen previously (Fig. 2) [17, 18]. Pemetrexed pharmacokinetics following pemetrexed administration with cisplatin were similar for both treatment arms (Table 4), suggesting that prior use of cisplatin induced no overt alterations in

Table 2 Pharmacokinetic parameters for total and free platinum following administration of cisplatin alone (CIS) or pemetrexed plus cisplatin (PEM + CIS)

	Geometric mean (CV%)			
	CIS[a] $N = 13$[b]		PEM + CIS[a] $N = 12$	
	Total	Free	Total	Free
C_{max} (µg mL^{-1})	2.99 (12)	1.71 (26)	2.90 (26)	1.86 (34)
$AUC_{(0-\infty)}$ (µg h mL^{-1})	330 (29)	4.08 (22)	297 (26)	3.83 (38)
CL (L h^{-1} m^{-2})	0.226 (29)	18.3 (22)	0.251 (25)	19.4 (38)
V_{ss} (L m^{-2})	40.4 (16)	30.9 (56)	42.9 (21)	30.5 (57)
$t_{1/2}$[c] (h)	92.3 (76.2–113)[d]	0.985 (0.458–2.22)[e]	88.6 (70.7–108)[d]	0.970 (0.433–2.63)[e]

Abbreviations: $AUC_{(0-\infty)}$ area under the concentration versus time curve from zero to infinity, *CIS* cisplatin, *CL* systemic clearance, C_{max} maximum observed drug concentration, *CV%* coefficient of variation expressed as percentage, *PEM* pemetrexed, $t_{1/2}$ half-life associated with the terminal rate constant, V_{ss} volume of distribution at steady state following intravenous administration

[a] Patients received study drug in treatment arm A or B

[b] One patient did not meet eligibility criteria relative to renal function and was discontinued after one cycle where the patient received cisplatin alone. An analysis conducted excluding that patient's data yields similar results; and, conclusions are unchanged

[c] Geometric mean (range)

[d] The beta half-life over the range of 4–72 h post-dose

[e] The beta half-life over the range of 2–8 h post-dose

Table 3 Least-squares geometric mean values and ratios for free and total platinum following administration of cisplatin alone or pemetrexed plus cisplatin

	Treatment	Free Platinum			Total Platinum		
		Arm A ($n = 6$)	Arm B ($n = 7$[a])	Overall ($N = 13$[a])	Arm A ($n = 6$)	Arm B ($n = 7$[a])	Overall ($N = 13$[a])
Dose-normalized C_{max} (μg mL^{-1})	CIS	0.013 (0.011, 0.015)	0.015 (0.013, 0.017)	0.014 (0.013, 0.016)	0.025 (0.022, 0.027)	0.025 (0.022, 0.028)	0.025 (0.023, 0.027)
	PEM + CIS	0.014 (0.011, 0.016)	0.017 (0.014, 0.020)	0.015 (0.014, 0.017)	0.021 (0.018, 0.023)	0.028 (0.025, 0.031)	0.024 (0.022, 0.026)
	Ratio[b]	1.03 (0.82, 1.30)	1.14 (0.91, 1.42)	1.08 (0.92, 1.27)	0.84 (0.73, 0.96)	1.12 (0.98, 1.27)	0.97 (0.88, 1.06)
Dose-normalized $AUC_{(0-\infty)}$ (μg h mL^{-1})	CIS	0.035 (0.030, 0.041)	0.033 (0.028, 0.038)	0.034 (0.030, 0.038)	3.32 (2.81, 3.93)	2.31 (1.97, 2.69)	2.77 (2.47, 3.10)
	PEM + CIS	0.027 (0.023, 0.031)	0.037 (0.032, 0.044)	0.031 (0.028, 0.035)	2.08 (1.76, 2.46)	2.75 (2.35, 3.22)	2.40 (2.14, 2.69)
	Ratio[b]	0.76 (0.63, 0.92)	1.14 (0.95, 1.37)	0.93 (0.82, 1.06)	0.63 (0.57, 0.69)	1.19 (1.08, 1.32)	0.87 (0.81, 0.93)

Treatment Arm A: cycle 1 = PEM + CIS; cycle 2 = CIS alone. Treatment Arm B: cycle 1 = CIS alone; cycle 2 = PEM + CIS

Abbreviations: $AUC_{(0-\infty)}$ area under the concentration–time curve from zero to infinity, C_{max} maximum observed drug concentration, *CIS* cisplatin, *PEM* pemetrexed

[a] One patient did not meet eligibility criteria relative to renal function and was discontinued after 1 cycle where the patient received cisplatin alone. An analysis conducted excluding that patient's data yields similar results; and, conclusions are unchanged

[b] Ratio is for the platinum pharmacokinetic parameter estimate resulting from PEM + CIS administered in combination in comparison to the parameter resulting from CIS administered alone; 90% confidence interval

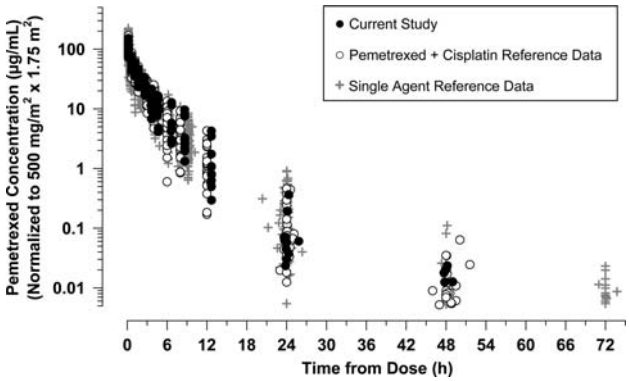

Fig. 2 Dose-normalized plasma pemetrexed concentrations versus time, comparison of current results to reference data

Table 4 Pharmacokinetic parameters for pemetrexed following administration of pemetrexed plus cisplatin

	Geometric Mean (CV%)		
	Treatment arm A	Treatment arm B	Overall
N	6	6	12
Dose[a] (mg)	832 (731–979)	846 (780–918)	839 (731–979)
Dose[a] (mg m^{-2})	512 (491–540)	505 (485–519)	505 (485–519)
BSA[a] (m^2)	1.63 (1.36–1.92)	1.67 (1.57–1.77)	1.65 (1.36–1.92)
$CrCL_{CG,std}$[a] (mL min^{-1})	88.6 (60.9–121)	94.0 (54.6–124)	91.3 (54.6–124)
C_{max} (μg mL^{-1})	109 (14)	110 (24)	109 (19)
$AUC_{(0-\infty)}$ μg h mL^{-1}	178 (17)	191 (32)	184 (24)
CL (mL min^{-1})	77.6 (24)	73.6 (30)	75.6 (26)
V_{ss} (L)	11.3 (16)	13.8 (19)	12.5 (20)
$t_{1/2}$[b] (h)	2.39 (2.13–2.52)	2.96 (2.63–3.57)	2.66 (2.13–3.57)

Abbreviations: $AUC_{(0-\infty)}$ area under the concentration versus time curve from zero to infinity, *BSA* body surface area, *CL* total body clearance of drug calculated after intravenous administration, C_{max} maximum observed drug concentration, $CrCL_{CG,std}$ creatinine clearance by standard Cockcroft–Gault method, *CV%* coefficient of variation expressed as percentage, $t_{1/2}$ half-life associated with the terminal rate constant, *Vss* volume of distribution at steady state following IV administration

[a] Arithmetic mean (range)

[b] Geometric mean (range)

pemetrexed pharmacokinetics (when given combined with cisplatin).

Toxicity

Relationships between the occurrence of AEs and systemic drug exposure of unbound platinum were not examined as there were no alterations of free platinum pharmacokinetics by pemetrexed. Two patients (15.4%) discontinued the study due to AEs: one patient with renal failure that was not considered to be related to study treatment, and the other

patient with reduced glomerular filtration rate which was considered to be related to study treatment.

A total of 12 patients had at least 1 TEAE, which was defined as an event that first occurred or worsened after randomization. The largest number of TEAEs, categorized as any grade and by system organ class was reported for gastrointestinal disorders (10 patients, 76.9%). The largest number of TEAEs by preferred term was reported for fatigue (7 patients, 53.8%), followed by nausea (6 patients, 46.2%).

Ten incidences of CTCAE grade 3 or 4 hematologic toxicities were reported for four patients, the most frequent being anemia (Table 5). Two grade 4 low neutrophil counts occurred in two patients. Eight grade 3 or 4 hematologic toxicities were considered by investigators as possibly related to study drug. There were a total of 16 nonhematologic CTCAE grade 3 or 4 events for four patients, including one patient with mucositis, one with thrombosis/embolism, one with febrile neutropenia and reduced creatinine clearance which were assessed by the investigator to be possibly related to the study drug. Infection, renal toxicity, musculoskeletal pain, diarrhea, and vomiting were also reported, with pain and vomiting possibly related to the study drug.

Responses

Ten of the 13 enrolled/treated patients were reported to have a best overall response of stable disease, while 2 patients had a best overall response of progressive disease. In addition, the patient who discontinued after one cycle of cisplatin due to ineligibility subsequently received five cycles of pemetrexed and cisplatin (off-study) and had a best overall response of stable disease.

Discussion

Pemetrexed (500 mg m^{-2}) in combination with cisplatin (75 mg m^{-2}) is approved worldwide to treat malignant pleural mesothelioma, based on results of the randomized phase 3 study comparing this regimen to cisplatin monotherapy [3]. Recently, the EMEA also approved this combination for the first-line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology [5]. The pharmacokinetics of total platinum and pemetrexed following administration of pemetrexed with cisplatin were evaluated previously using population pharmacokinetic methods [6]. Those analyses showed that concomitant cisplatin administration had no significant influence on pemetrexed pharmacokinetics and concomitant pemetrexed administration had no significant influence on cisplatin (i.e., platinum) pharmacokinetics.

The main objective of the present study was to evaluate whether pemetrexed has any influence on free platinum pharmacokinetics. The assessment of exposure to free platinum (C_{max} and AUC) affords an opportunity to assess whether there was any alteration in free platinum

Table 5 Common terminology criteria for adverse events (v3.0) toxicities by treatment cycle ($N = 12$)

Toxicity (grade 3/4)	CIS alone		PEM + CIS		PEM + CIS
	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycles 3–6
Hematologic (*n*)					
Anemia		1			5
Neutropenia					2
Thrombocytopenia					2
Nonhematologic (*n*)					
Creatinine, reduced clearance					1
Diarrhea					1
Fatigue					1
Febrile neutropenia	1				
Hypokalemia					1
Infection, upper respiratory				1	2
Mucositis					1
Muscle weakness	1				
Pain, muscoskeletal-back					2
Pulmonary-NOS					1
Renal-NOS					1
Thrombosis/embolism	1				
Vomiting				1	

One event continuing over several cycles was repeated in the table in each cycle it was present

Abbreviations: *CIS* cisplatin, *NOS* not otherwise specified, *PEM* pemetrexed

pharmacokinetics indicative of a drug–drug interaction. The pharmacokinetics of pemetrexed administered with cisplatin was also evaluated. To correct for bias resulting from total platinum accumulation as a consequence of its long half-life (i.e., carry-over effect), a two-arm, crossover design with two dosing sequences was utilized. The study showed that there were no clinically relevant alterations in platinum pharmacokinetics for either free platinum or total platinum when cisplatin was administered in combination with pemetrexed relative to when cisplatin was administered alone. The combination of pemetrexed 500 mg m^{-2} and cisplatin 75 mg m^{-2} was well-tolerated by patients with squamous cell HNC. Of the 13 patients enrolled and treated in this study, there were no complete responses. Eleven patients had a best overall response of stable disease, and two patients had a best overall response of progressive disease.

Pemetrexed has been shown to be active in HNC. In a phase II study conducted prior to the programmatic implementation of vitamin supplementation on pemetrexed studies, Pivot et al. [8] administered pemetrexed 500 mg m^{-2} to 35 patients with squamous cell HNC and observed a 26.5% objective response and 44.1% stable disease. Grade 3 or 4 hematological toxicities were neutropenia (68.6%) and anemia (34.3%). Additionally, febrile neutropenia occurred in 11% of patients, with two patient deaths from neutropenic sepsis. Subsequent pemetrexed studies showed that these toxicities can be managed with folic acid and vitamin B_{12} supplementation [3, 5, 18, 19]. The lower toxicity seen in the current study is a reflection of the use of folic acid and vitamin B_{12} supplementation.

In general, the CIs for the ratios of free and total platinum exposures showed less than 20% difference for the exposures following cisplatin administered alone compared to cisplatin administered with pemetrexed. In the case of C_{max} for free platinum, the change was within 21% (the upper CI for the ratio was 1.27, which for a log-normal distribution, is a 21% increase). For most drugs, changes of approximately 20% or less are considered non-clinically significant. Although a clear understanding of the change that would be clinically relevant for platinum is lacking, and despite the limitations due to intersubject variability and the small sample size of the current study, it may be reasonable to conclude that no clinically significant alterations in total platinum pharmacokinetics were observed based on the ratios and 90% CIs seen in this study. Further, these results show that pemetrexed administered with cisplatin did not alter platinum protein binding or free platinum concentrations. Total platinum pharmacokinetics was similar to those seen in previous studies where pemetrexed was administered in combination with cisplatin [9, 17].

Additionally, there were no discernible differences in pemetrexed pharmacokinetics seen between the two treatment arms. Pemetrexed plasma concentrations following the end of infusion declined rapidly with half-lives ranging from 2.1 to 3.6 h. Pemetrexed pharmacokinetics in the current study was similar to those observed previously for single-agent administration [16, 18, 20] and in combination with cisplatin [6, 17].

Overall, the toxicities seen during this study were not unexpected and were consistent with the previously established safety profile of pemetrexed 500 mg m^{-2} administered in combination with cisplatin 75 mg m^{-2}. Five patients had CTCAE grade 3 or grade 4 events, the most frequent being low hemoglobin. Two patients discontinued the study due to AEs, one due to decreased glomerular filtration rate attributed to the study drug and the other due to renal failure that was not attributed to the study drug.

In summary, this study showed that pemetrexed administered with cisplatin does not alter platinum protein binding; and therefore, does not alter free platinum concentrations, nor does the use of cisplatin seem to affect pemetrexed pharmacokinetics. Comparison of the present pharmacokinetic data with those from previous studies of single-agent pemetrexed and those from previous studies with pemetrexed plus cisplatin administered in combination suggest that, overall, cisplatin co-administration will not have a major impact on pemetrexed pharmacokinetics. Therefore, the toxicity profile of the combination of pemetrexed and cisplatin is rather more likely a result of combined pharmacodynamic effects than a result of any alteration in the pharmacokinetics of either drug.

The combination of pemetrexed 500 mg m^{-2} and cisplatin 75 mg m^{-2} was well tolerated by patients with squamous cell HNC. These findings are important because cisplatin is the cornerstone of many combination chemotherapy regimens used to treat patients with HNC [7]. These findings are also relevant to other cancers where the pemetrexed plus cisplatin combination was used: MPM, where this combination is now the established standard of care, and for first-line NSCLC, for which this combination was recently approved by the EMEA. A decrease in free platinum exposure could have a negative effect on efficacy-related outcome for patients treated with the combination, while an increased exposure could result in unexpected or increased likelihood of toxicities. Overall, the toxicities seen during this study were not unexpected and were consistent with the previously established safety profile of this combination.

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References

1. Shih C, Habeck LL, Mendelsohn LG, Chen VJ, Schultz RM (1998) Multiple folate enzyme inhibition: mechanism of a novel pyrrolopyrimidine-based antifolate LY231514 (MTA). Adv Enzyme Regul 38:135–152
2. Hanauske AR, Chen V, Paoletti P, Niyikiza C (2001) Pemetrexed disodium: a novel antifolate clinically active against multiple solid tumors. Oncologist 6:363–373
3. Vogelzang NJ, Rusthoven JJ, Symanowski J et al (2003) Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21:2636–2644
4. Hanna N, Shepherd FA, Fossella FV et al (2004) Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589–1597
5. Scagliotti G, Parikh P, von Pawel J et al (2008) Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol, in press
6. ALIMTA® (2007) Pemetrexed for injection (package insert). Eli Lilly and Company, Indianapolis, IN, USA. Available via: http://pi.lilly.com/us/alimta-pi.pdf. Accessed 08 May 2008
7. The NCCN Clinical Practice Guidelines in Oncology™ (2007) Head and Neck Cancers (Version 1). National Comprehensive Cancer Network, Inc. Available via: http://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf. Accessed 08 May 2008
8. Pivot X, Raymond E, Laguerre B et al (2001) Pemetrexed disodium in recurrent locally advanced or metastatic squamous cell carcinoma of the head and neck. Br J Cancer 85:649–655
9. Thodtmann R, Depenbrock H, Dumez H et al (1999) Clinical and pharmacokinetic phase I study of multitargeted antifolate (LY231514) in combination with cisplatin. J Clin Oncol 17:3009–3016
10. Eli Lilly and Company (2006) A study for patients with head and neck cancer [H3E-MC-JMHR]. ClinicalTrials.gov. Available via: http://www.clinicaltrials.gov/ct2/show/NCT00415194?term=H3E-MC-JMHR&rank=1. Accessed 08 May 2008
11. PLATINOL®-AQ (1999) Cisplatin for injection (package insert). Bristol-Myers Squibb Company, Princeton, NJ, USA. Available via: http://165.112.6.82/dailymed/fda/fdaDrugXsl.cfm?id=4915&type=display. Accessed 08 May 2008
12. Cancer Therapy Evaluation Program (2006) Common terminology criteria for adverse events v3.0 (CTCAE). National Cancer Institute. Available via: http://ctep.cancer.gov/forms/CTCAEv3.pdf. Accessed 08 May 2008
13. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
14. Vermorken JB, van der Vijgh WJ, Klein I et al (1984) Pharmacokinetics of free and total platinum species after short-term infusion of cisplatin. Cancer Treat Rep 68:505–513
15. Vermorken JB, van der Vijgh WJ, Klein I et al (1986) Pharmacokinetics of free and total platinum species after rapid and prolonged infusions of cisplatin. Clin Pharmacol Ther 39:136–144
16. Latz JE, Chaudhary A, Ghosh A, Johnson RD (2006) Population pharmacokinetic analysis of ten phase II clinical trials of pemetrexed in cancer patients. Cancer Chemother Pharmacol 57:401–411
17. Musib LC, Schneck KB, Thomas M et al (2008) Pharmacokinetics of platinum (total and free) and pemetrexed for pemetrexed doses of 500 mg/m^2 to 900 mg/m^2 administered in combination with cisplatin 75 mg/m^2. ICACT, abstract PO 215. Available via: http://www.icact.com/Abstract_Book_2008.pdf. Accessed 08 May 2008
18. Takimoto CH, Hammond-Thelin LA, Latz JE et al (2007) Phase I and pharmacokinetic study of pemetrexed with high-dose folic acid supplementation or multivitamin supplementation in patients with locally advanced or metastatic cancer. Clin Cancer Res 13:2675–2683
19. Niyikiza C, Baker SD, Seitz DE et al (2002) Homocysteine and methylmalonic acid: markers to predict and avoid toxicity from pemetrexed therapy. Mol Cancer Ther 1:545–552
20. Rinaldi DA, Kuhn JG, Burris HA et al (1999) A phase I evaluation of multitargeted antifolate (MTA, LY231514), administered every 21 days, utilizing the modified continual reassessment method for dose escalation. Cancer Chemother Pharmacol 44:372–380