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SHORT COMMUNICATION

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Pharmacokinetics of paclitaxel administered in combination with cisplatin, etoposide and bleomycin in patients with advanced solid tumours

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Abstract *Purpose*: To evaluate the pharmacokinetics of paclitaxel and cisplatin administered in combination with bleomycin and etoposide and Granulocyte Colony-Stimulating Factor (G-CSF) in patients with advanced solid tumours. *Methods*: Patients were recruited to a phase I trial where escalating doses of paclitaxel (125 to 200 mg/m^2) were administered in combination with etoposide 100 or 120 mg/m^2, and fixed dose of cisplatin 20 mg/m^2 and bleomycin 30 mg, with the concomitant use of G-CSF. Paclitaxel (3-h infusion) was followed by 1-h etoposide, 4-h cisplatin and 30-min bleomycin infusions, respectively. Pharmacokinetics sampling for paclitaxel analysis was performed in ten patients from dose levels II–V. *Results*: The mean paclitaxel area under the plasma concentration-versus-time curves (AUC) for the 125-mg/m^2 dose level (II) was 7.0 ± 3.6 h μmol^{-1} l^{-1}, for the 175-mg/m^2 dose level (III) 10.6 ± 2.8 h μmol^{-1} l^{-1}, for the 200-mg/m^2 dose level (IV) it was 16.0 ± 5.0 h μmol^{-1} l^{-1}, and for the 175-mg/m^2 dose level (V) it was 12.5 ± 6.1 h μmol^{-1} l^{-1}. The mean peak plasma concentration (C_{max}) values for dose levels II–V were 1.9 ± 1.1 μmol/l, 3.4 ± 1.2 μmol/l, 4.3 ± 1.0 μmol/l and 3.8 ± 1.2 h μmol/l, respectively. *Conclusion*: In this study, relevant pharmacokinetic parameters of paclitaxel like AUC, C_{max} and the paclitaxel plasma concentration above the pharmacologically relevant 0.1-μmol/l threshold concentration ($t > 0.1$ μM) when administered in combination with cisplatin, etoposide and bleomycin (PEB) were not statistically different from paclitaxel data of historical controls. However, given the trial design, pharmacokinetic interactions between the agents cannot be excluded.

Key words Bleomycin · Cisplatin · Etoposide · Paclitaxel · Pharmacokinetics

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Introduction

Cisplatin is the cornerstone of several chemotherapy combinations including PEB (cisplatin, etoposide and bleomycin) or PEI (cisplatin, etoposide and ifosfamide) for the treatment of germ-cell tumours and which results in long-term disease-free survival in the majority (70–80%) of patients [5, 8, 22]. In order to optimize treatment, a prognostic factor classification has been proposed recently, which stratifies patients into a good prognosis, an intermediate prognosis and a poor prognosis group [11]. For patients with high-risk prognosis, associated with an increase risk of relapse, high-dose chemotherapy with peripheral stem cell support is currently being investigated [4]. However, this approach is not considered to be necessary for use in the intermediate-risk group because it would imply overtreatment. For this small group of patients, it would be reasonable to investigate the addition of paclitaxel, a taxane derivative with a unique mechanism of action, to the PEB regimen. Paclitaxel has demonstrated pronounced efficacy in several malignancies, including non-small cell lung cancer, head and neck cancer and advanced cancer of the urothelium, and has been licensed for the treat-

ment of advanced breast and ovarian cancer. The main toxicities of paclitaxel consist of neutropenia, alopecia, peripheral neurotoxicity, cardiac effects and hypersensitivity reactions [17]. Moreover, paclitaxel showed a considerable cytotoxic effect in teratocarcinoma cells resistant to cisplatin in vitro [3]. In addition, the DNA damage caused by cisplatin is less well resolved when paclitaxel is administered prior to cisplatin. Paclitaxel has been studied as a single agent in patients with cisplatin-refractory or relapsed malignant germ-cell tumours and has shown activity in 8/31 and 6/24 patients [1, 2, 3]. Our aim is to develop a PEB-paclitaxel treatment schedule for patients with advanced germ-cell cancer. However, in view of the expected slow recruitment of patients with this disease, we undertook a dose-finding study of paclitaxel in combination with PEB in patients with undifferentiated carcinoma or poorly differentiated adenocarcinoma of unknown primary site (CUP/ACUP). For these patients, cisplatin-based combinations are also considered to be appropriate chemotherapy [7]. The objective of this study was to describe the pharmacokinetics of paclitaxel when followed by a fixed dose of PEB.

Patients and methods

Patients were enrolled into a multicentre study, the preliminary results of which have been published recently [23]. Given the pharmacological relevance of paclitaxel kinetics, we decide to investigate the pharmacokinetics of paclitaxel in the patients who were admitted to The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital site at a later stage. Patients were eligible if they had histologically or cytologically proven solid tumours (of known or unknown primary site) for which an indication for chemotherapy existed and the combination of bleomycin, etoposide and cisplatin was feasible. In brief, eligibility criteria were the following: age < 50 years, a World Health Organization (WHO) or Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate bone marrow function (white blood cell count (WBC) $\geq 3.0 \times 10^2$/l, platelets $\geq 100 \times 10^2$/l), adequate hepatic function (serum bilirubin $\leq 1.25 \times$ the upper normal limit, SGOT $\leq 2 \times$ the upper normal limit and $\leq 3 \times$ the upper normal limit in the case of liver metastases), and adequate renal function (creatinine clearance > 60 ml/min). All patients had bidimensionally measurable or evaluable disease and responses were determined according to standard WHO criteria [20]. Antitumour activity was evaluated after two cycles, and patients with a response or stable disease continued up to four cycles. Pretreatment evaluation consisted of a complete history and physical examination, routine chest X-ray, complete blood cell count, serum chemistry analysis, electrodiogram and neurological assessment. All pretreatment studies were performed within 2 weeks before start of therapy. Haematological toxicity was assessed by measurement of full blood counts with weekly differentials. Written informed consent was obtained from all patients before study entry. The protocol was approved by the medical ethics committee of the hospital. The study was conducted in accordance with the Declaration of Helsinki and its recent amendments (Somerset West 1996).

Drug administration

Chemotherapy consisted of cycles at 21-day intervals of escalating doses of paclitaxel (dose level I: 75 mg/m^2, dose level II: 125 mg/m^2, dose level III: 175 mg/m^2, dose level IV: 200 mg/m^2, dose level V: 175 mg/m^2) and PEB. On day 1, 3-h paclitaxel was given 1 h after the end of the infusion by a 30-min infusion of etoposide, subsequently by a 4-h cisplatin infusion and 2 h after the cisplatin administration by a 30-min infusion of bleomycin. Paclitaxel (Bristol-Myers Squibb, Princeton, N.J., USA) was supplied as concentrated sterile solution (6 mg/ml) in a 5-ml vial in polyoxyethylated castor oil (Cremophor EL) and dehydrated alcohol (1:1, v/v). They were diluted before use with 500 ml 0.9% sodium chloride to paclitaxel concentrations not exceeding 1.2 mg/ml. Standard premedication consisted of dexamethasone (20 mg orally 12 h and 6 h prior to paclitaxel infusion), clemastine (2 mg intravenously 30 min prior to paclitaxel infusion) and cimetidine (300 mg intravenously 30 min prior to paclitaxel infusion). On day 1 only, paclitaxel was administered as a continuous 3-h intravenous infusion through an IVAC IV administration set with low sorbing tubing (IVAC, San Diego, Calif., USA) and an IVEX-II vented filter set (0.22 μm; Millipore, Malsheim, France) was used for in-line filtration. The PEB schedule consisted of cisplatin, etoposide and bleomycin. Cisplatin (Abic, Netanya, Israel) was supplied as a concentrated sterile solution (50 mg/ml) in sodium chloride, citric acid and water for injection. Before cisplatin administration, prehydration was given with 1000 ml of normal saline within 4 h. Cisplatin 20 mg/m^2 was administered in 250 ml hypertonic saline (3% NaCl) as a 4-h continuous infusion on days 1–5. Posthydration consisted of 3000 ml of normal saline, with 60 mmol potassium chloride and 1.5 g magnesium sulfate salt as additives. Etoposide (Vepesid, Bristol-Myers Squibb) was administered as a 1-h continuous intravenous infusion in 500 ml if normal saline (120 mg/m^2 every other day on days 1, 3 and 5; 100 mg/m^2 daily on days 1–5 at dose level V) of each treatment cycle. Bleomycin (Lundbeck, Amsterdam, The Netherlands) 30 mg was administered in 100 ml of normal saline as a 1-h intravenous infusion starting on day 1 of the first treatment cycle and continuing for every week thereafter during the treatment cycles. Granulocyte Colony-Stimulating Factor (G-CSF; Neupogen, filgrastim, Breda, The Netherlands) 5 μg/kg was administered to each patient subcutaneously on days 6–15.

Pharmacokinetic analysis

Complete paclitaxel plasma concentration-time curves were obtained during the first course. Samples were collected by intravenous sampling from the arm contralateral to the one receiving the paclitaxel infusion at 15 different time points: immediately before the infusion, 1 h and 2 h during infusion, at the end of infusion and at 0.08, 0.25, 0.5, 1, 2, 3, 6, 8, 10, 18 h and 24 h after cessation of the infusion. Plasma was obtained by immediate centrifugation (5 min, 1500 *g*) of the samples and was stored at −20 °C until analysis. Analysis for paclitaxel was executed by a sensitive high-performance liquid chromatographic (HPLC) method as previously described [9]. After the first patient was entered at dose level II for paclitaxel measurement, it was decided to also study cisplatin pharmacokinetics in the following patients. Samples for cisplatin measurement were collected at nine time points on day 1: immediately before the infusion, 1 h and 2 h during and at the end of the infusion, and at 0.5, 1, 2, 4 h and 12 h after the end of the infusion. Plasma was obtained by immediate centrifugation (5 min, 1500 *g*) of the samples and a part was transferred directly to an MPS-1 device provided with a YMT-30 filter (Amicon Division, W.R. Grace, Danvers, Mass., USA), which was centrifuged for 10 min at 1500 *g*. Thereafter, plasma and plasma ultrafiltrate were stored at −20 °C until analysis. Platinum levels were analysed using a validated method based on Zeeman flameless atomic absorption spectrophotometry and were recalculated as cisplatin concentrations [20]. Pharmacokinetic parameters for paclitaxel and cisplatin were calculated by noncompartmental methods. The terminal elimination rate constant (k_{el}) was determined by least-squares regression

analysis of terminal log-linear parts of the plasma concentration-versus-time curve (at least three points were used). The terminal half-life ($t_{1/2}$) was calculated as $0.693/k_{el}$. The total are under the curve ($AUC_{0\to\infty}$) was obtained by the linear trapezoidal rule up to the last sampling point, with extrapolation of the terminal phase to infinity (C_{last}/k_{el}), where C_{last} is the measured concentration. Total body clearance (CL) was calculated by the formula:

$CL = dose/AUC_{0\to\infty}$. The peak plasma concentration (C_{max}) was the highest measured value. The time spent above the paclitaxel plasma threshold concentration of 0.1 μmol/l ($t > 0.1\ \mu M$) was derived graphically.

Pharmacodynamics

The haematological toxicity was evaluated as percentage decrease (%D) in granulocytes (absolute neutrophil count, ANC) after the first course, using the following equation:

$$\%D = \{(\text{pretreatment value} - \text{nadir value})/\text{pretreatment value} \times 100\}$$

The decrease in ANC was related with the pharmacokinetic parameters AUC and $t > 0.1\ \mu M$ using scatter plots, and pharmacokinetic-pharmacodynamic relationships were modelled by using the sigmoidal maximum effect (E_{max}) equation:

$$E\ (\%\ \text{change}) = (E_{max} \cdot P^H)/(P_{50}^H + P^H)$$

where E_{max} represents the maximal elicitable effect, and P represents the pharmacokinetic parameter of interest. P_{50} is the value of the parameter by which 50% of E_{max} is elicited. The exponent H, also known as the Hill constant, determines the sigmoidity of the curve.

Results

Pharmacokinetics were performed in ten patients in this study, who were entered at our hospital from dose levels II to V. In brief, their characteristics were: median age 38 years (range 23–48 years), median WHO performances status 1 (range 0–1). Seven patients had ACUP, two patients had an extragonadal germ-cell tumour, and one patient had an adenoidcystic carcinoma of the trachea. The median number of metastases was 2 (sites primarily consisting of lung, bone, pleura or lymph nodes). A total of 35 courses was administered, with a median number of 4 (range 2–4) per patient. In general, treatment was well tolerated, with two episodes of neutropenic fever lasting 3 and 4 days, respectively (at dose level IV). A partial response was seen in one of the two patients with extragonadal germ-cell cancer, while three out of seven ACUP patients showed a (marker-negative) partial response.

The pharmacokinetic results of the different paclitaxel doses and those of historical controls from our own data set are listed in Table 1. These historical control data were selected because paclitaxel was administered at comparable administration dosages, which would make comparisons more appropriate. No statistically significant differences (Mann-Whitney tests, $P > 0.05$) were observed for any of the investigated paclitaxel pharmacokinetic parameters (AUC, C_{max}, CL and $t > 0.1\ \mu M$) when compared with the data from these controls. Mean paclitaxel concentration-versus-time curves are depicted in Fig. 1. When the dose of paclitaxel was increased from 125 (dose level II) to 175 mg/m^2 and 200 mg/m^2, the mean AUC increased disproportionally with decreasing clearances. This phenomenon is indicative of the non-linear pharmacokinetic behaviour of paclitaxel. However, the interindividual variability is large, leading to no significance between the different dose levels.

After one patient had already been treated at dose level II (125 mg/m^2 of paclitaxel), it was also decide to study cisplatin pharmacokinetics. The one remaining patient at dose level II had a free cisplatin AUC of 4.0 h μmol^{-1} l^{-1}, C_{max} 0.98 μmol/l and cisplatin CL of

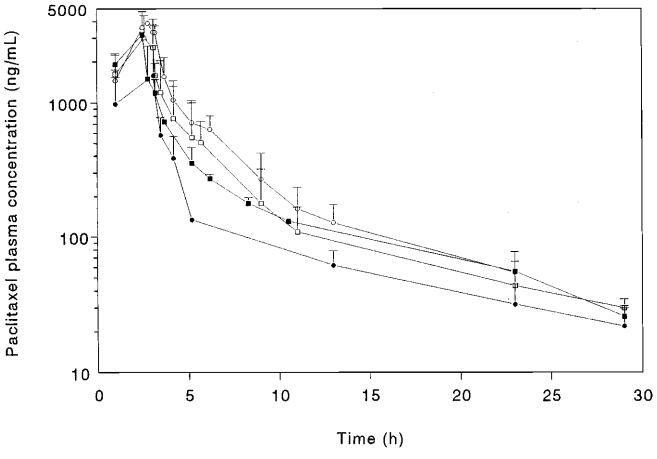

Fig. 1 Mean paclitaxel concentration-versus-time curves for the different dose levels. ● level I and II; ■ level III; ○ level IV; □ level V

Table 1 Pharmacokinetic parameters of 3-h paclitaxel (*P*) in escalating doses administered in combination with bleomycin, etoposide (*E*), cisplatin and granulocyte colony-stimulating factor. Historical controls (*HC*) are data from [10], 3-h paclitaxel (*P*) and carboplatin (*C*). *AUC* area under the concentration-versus-time curves, C_{max} peak plasma concentration, *CL* total body clearance, *SD* standard deviation

Dose (level)	AUC (±SD; h μmol^{-1} l^{-1})	C_{max} (±SD; μmol/l)	CL (±SD; l h^{-2} m^{-2})	$t > 0.1\ \mu M$ (±SD; h)	*n*
125 mg/m^2 P + 360 mg/m^2 E (II)	7.0 ± 3.6	1.9 ± 1.1	24.5 ± 12.7	9.3 ± 3.9	2
175 mg/m^2 P + 360 mg/m^2 E (III)	10.6 ± 2.8	3.4 ± 1.2	20.1 ± 5.3	14.6 ± 0.2	2
200 mg/m^2 P + 360 mg/m^2 E (IV)	16.0 ± 5.0	4.3 ± 1.0	15.8 ± 5.2	17.6 ± 5.7	3
175 mg/m^2 P + 500 mg/m^2 E (V)	12.5 ± 6.1	3.8 ± 2.1	18.8 ± 7.6	12.6 ± 5.0	3
HC 125 mg/m^2 P + 300 mg/m^2 C	7.0 ± 2.2	2.2 ± 1.2	22.3 ± 8.2	9.7 ± 4.3	6
HC 175 mg/m^2 P + 300 mg/m^2 C	12.3 ± 3.1	3.4 ± 0.7	19.5 ± 6.9	14.0 ± 3.6	7
HC 200 mg/m^2 P + 300 mg/m^2 C	17.4 ± 4.9	5.3 ± 1.1	14.7 ± 5.5	16.3 ± 7.7	7

14.4 l h^{-2} m^{-2}. The mean cisplatin AUC for dose level III was 4.3 ± 1.0 h μmol^{-1}/l^{-1}, for dose level IV 5.7 ± 0.4 h μmol^{-1} l^{-1}, and for dose level V it was 5.3 ± 1.1 h μmol^{-1} l^{-1}. The mean C_{max} values were 1.1 ± 0.3 h μmol/l, 1.1 ± 1.0 h μmol/l and 1.3 ± 0.3 μmol/l for dose levels III, IV and V, respectively. No significant sigmoidal E_{max} or linear relationships were found between haematological toxicity (% decrease in ANC) and paclitaxel pharmacokinetic parameters such as AUC or $t > 0.1$ μM.

Discussion

This study is part of a multi-institutional trial designed to assess the feasibility of paclitaxel in combination with the standard PEB regimen for use as first-line treatment in patients with undifferentiated CUP or ACUP. We now present pharmacokinetic data of paclitaxel when given in combination with PEB. These data were compared with those of patients treated previously in our Institute with paclitaxel followed by carboplatin [10]. This group of historical controls was selected because paclitaxel was administered in the same dosages as used here in the present study, which makes the data comparable. This is of importance, since paclitaxel demonstrates nonlinear behaviour, which makes a pharmacokinetic comparison with different dosages of paclitaxel inappropriate. Furthermore, there are no other studies available which could provide pharmacokinetic data of both paclitaxel and cisplatin at the dosages used in the present study. The paclitaxel AUC, C_{max} and $t > 0.1$ μM data as obtained here were not statistically significant from the historical controls for the studies dosages. Furthermore, the mean $t > 0.1$ μM was greater than 15 h in four out of ten patients. Our group has demonstrated previously that $t > 0.1$ μM exceeding 15 h was associated with prolonged survival in patients with non-small cell lung cancer who received the combination of paclitaxel with carboplatin [10]. As can be concluded from these results, clinically relevant levels and exposure times of paclitaxel were achieved in combination with the PEB schedule. In addition, the pharmacokinetic parameters of cisplatin in this study were also similar to those described previously [19]. Originally, the primary purpose of the study in which these patients were included was to assess the feasibility of the addition of escalating dosages of paclitaxel to a fixed dose of PEB chemotherapy, not to study its pharmacokinetics. From this perspective, it is important to note that sequence-dependent pharmacokinetic effects have been reported for paclitaxel and cisplatin. The pharmacological exposure to paclitaxel was 33% higher when cisplatin preceded paclitaxel [18]. We were not able to detect this in our study. However, the design, the drug administration schedule and the time interval between the administration of paclitaxel and cisplatin were different from those in our study, which may partly explain this discrepancy.

In addition, the co-administration and the possible influence of the administration of etoposide on paclitaxel pharmacokinetics remains unclear. Paclitaxel is cleared by hepatic metabolism and biliary excretion, while recent data suggest that epotoside is also metabolized by the cytochrome P450 3A4 enzyme [14, 15]. Furthermore, the paclitaxel vehicle Cremphor EL has been demonstrated to inhibit the elimination of etoposide [6]. In another in vitro study, etoposide administered before paclitaxel yielded antagonistic interactions [12]. On the other hand, etoposide preceding paclitaxel was shown to be more effective than the administration of both agents at the same time [16]. Thus, given the design of the present study, the absence of (sequence-dependent) pharmacokinetic interactions cannot be fully excluded in this study.

In conclusion, compared with historical data, it was found that pharmacologically relevant paclitaxel pharmacokinetic parameters $t > 0.1$ μM, AUC and C_{max} are not affected by the administration in combination with PEB. The results show that clinically effective paclitaxel concentrations are achieved and demonstrate the feasibility of paclitaxel administered in combination with PEB. The safety and activity of this regimen should be tested, and a randomized trial by the European Organization on Research and Treatment of Cancer (EORTC) and collaborative groups is planned.

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