Pegylated liposomal doxorubicin hydrochloride (PLD) and paclitaxel in recurrent or metastatic head and neck carcinoma: a phase I/II study conducted by the Hellenic Cooperative Oncology Group (HeCOG)

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A phase I pharmacokinetics and dose-finding study and a phase II study of the combination of pegylated liposomal doxorubicin HCl (PLD) and paclitaxel were conducted in patients with recurrent or metastatic head and neck cancer (HNC). Sixty patients with recurrent or metastatic disease were enrolled in the study: 11 patients in the phase I study and 49 patients in the phase II study. In the phase I study, the initial dose level of PLD was 35 mg/m^2 as a 1-h infusion with escalating increments of 5 mg/m^2 until the maximum tolerated dose (MTD) was reached. A fixed dose of paclitaxel (175 mg/m^2) was administered as a 3-h infusion. The combination was administered every 28 days. Pharmacokinetic studies performed on 10 patients indicated that the sequence of drug administration did not cause clinically significant modifications in the pharmacokinetics of either drug. The MTD for PLD was 45 mg/m^2 (dose level 3) and the dose-limiting toxicity was febrile neutropenia, occurring in three of five patients. The phase II dose of PLD was 40 mg/m^2 (dose level 2) and a total of 214 cycles were delivered. Grade 3 or 4 neutropenia was observed in 26% patients and febrile neutropenia occurred in 16% of patients. Grade 3 palmar–plantar erythrodysesthesia (PPE) was recorded in only one patient. The overall response rate was 28% for patients with non-nasopharyngeal tumors [95% confidence interval (CI) 15–45%] and 28.6% for the study population (95% CI 17–43%). The median survival for the study population was 9.7 months; 1-year survival was 38%. We conclude that the recommended dose for the combination of PLD and paclitaxel is 40 and 175 mg/m^2 every 28 days, without granulocyte colony stimulating factor support. The combination of paclitaxel with PLD demonstrated activity in recurrent or metastatic HNC, a favorable toxicity profile and relative ease of administration. ***Anti-Cancer Drugs*** **15:479–487 © 2004 Lippincott Williams & Wilkins.**

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Introduction

Pegylated liposomal doxorubicin hydrochloride (PLD) (Caelyx; Schering-Plough, Kenilworth, NJ) has been developed to target drug delivery to cancer cells, while reducing some of the toxicities (myelosuppression, alopecia and cardiotoxicity) associated with conventional doxorubicin. Doxorubicin interferes with topoisomerase–DNA complexes, preventing the completion of the religation in the ligation–religation reaction of DNA synthesis.

A number of phase I and II studies have shown that the combined administration of PLD with radiotherapy appears to be a highly effective approach to the treatment of locally advanced and recurrent head and neck cancer (HNC) [1–3]. The combination of paclitaxel with PLD has been explored in various malignancies [4,5]. In a recent dose-escalation phase I study in patients with recurrent or metastatic HNC, the maximum tolerated dose (MTD) for PLD was 50 mg/m^2 every 3 weeks, with an overall response rate of 33% [6].

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Paclitaxel (Taxol; Bristol-Myers Squibb, New York, NY) inhibits microtubule depolymerization, blocking dividing cells at the G_2/M phase of the cell cycle [7]. Several phase I and II studies have demonstrated that, as a single agent, paclitaxel has significant activity in HNC with response rates ranging between 20 and 40% [8–10]. The combination of gemcitabine and paclitaxel produced an overall response rate of 41% [11]. Paclitaxel in combination with cisplatin, carboplatin, 5-fluorouracil (5-FU) and ifosfamide demonstrates response rates between 33 and 62% depending on the selected patient population [12–19]. However, platinum/paclitaxel combinations are excessively myelotoxic [16,19].

Complementary mechanisms of action and distinct toxicity profiles combined with the demonstrated efficacy of both agents in the treatment of HNC make the combination of PLD and paclitaxel an interesting regimen for trial. The primary end point of this study was to determine the MTD, response rate and toxicity profile of escalating doses of PLD when administered with a fixed dose of paclitaxel in patients with recurrent and/or metastatic HNC. The secondary objective was to determine the pharmacokinetics of paclitaxel and PLD administered in combination.

Patients and methods

Inclusion criteria

Patients with histologically proven, recurrent and/or metastatic carcinoma of the head and neck, not curable by surgery or radiotherapy, were enrolled. Patients aged ≥ 18 years with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 and a life expectancy of ≥ 3 months were eligible for the study. Patients with squamous cell carcinoma as well as undifferentiated or non-keratinizing carcinoma of the nasopharynx were included. Measurable disease outside of pre-irradiated areas was required for inclusion. The disease could be located in previously irradiated areas provided that subsequent progression was documented. Previous chemotherapy prior to or concomitant with radiation as a locoregional modality was allowed, if administered ≥ 1 year before entry. Patients with prior chemotherapy for recurrent or metastatic disease were excluded. All patients gave an informed consent. The protocol for the study was approved by the Hellenic Cooperative Oncology Group (HeCOG) protocol review committee and by the institutional review boards.

Study design

Within 1 week of study entry, all patients had a complete history and physical examination, complete blood count, serum chemistries (liver and renal function tests and electrolytes), urinalysis, and ECG. Within 1 month of study entry, all patients had a chest radiograph and computed tomography (CT) or magnetic resonance imaging (MRI) scans of the head and neck, as indicated. Patients with measurable or assessable disease located in the lungs, abdomen or bone received baseline CT or bone scans.

Phase I study

The chemotherapy regimen consisted of 28-day cycles of PLD in escalating doses, without intra-patient dose escalation, and a fixed dose of paclitaxel. PLD was dissolved in 250 ml of 5% dextrose and administered over 60 min on day 1 followed by paclitaxel at a dose of 175 mg/m^2 over 3 h on day 1. All patients were premedicated as follows: dexamethasone 20 mg i.v. 12 and 6 h before paclitaxel infusion, diphenhydramine 50 mg i.v. 1 h before paclitaxel and cimetidine 300 mg i.v. 1 h before paclitaxel infusion. Standard antiemetics were used at the discretion of the treating physician with a recommendation to use a 5-HT$_3$ antagonist. Granulocyte-colony stimulating factor (G-CSF, 5 μg/kg/day) was administered if absolute neutrophil count (ANC) was $< 500/\mu l$ or in the case of febrile neutropenia.

PLD dose escalation

PLD was administered at an initial dose of 35 mg/m^2. The dose was subsequently escalated by 5 mg/m^2 per dose level. Cohorts of at least three patients were treated at each dose level. Dose escalation could occur if no patients had DLT after the first cycle. DLT was defined as grade 4 neutropenia, thrombocytopenia or febrile neutropenia; grade 3 thrombocytopenia associated with a bleeding episode; or any non-hematologic grade 3 or 4 toxicity (except for alopecia and nausea). If one of three patients had DLT, two more patients were enrolled at the same dose level (maximum of five patients). At any dose level, if more than 50% of patients developed neutropenia as the DLT and/or more than 30% of patients developed any other DLT, that dose level was defined as the MTD and the dose level immediately below was recommended for phase II evaluation.

Dose modifications

Dose reductions for PLD were made when granulocytopenia or thrombocytopenia had been present for ≥ 7 days or in case of febrile neutropenia. Dose reduction for paclitaxel was performed in case of non-hematologic toxicity specific for the drug, i.e. neurotoxicity. The standard levels that were used in modifying the dose of paclitaxel were as follows: level 0, 175 mg/m^2; level 1, 135 mg/m^2; level 2, 100 mg/m^2; level 3, 80 mg/m^2. Any patient who did not tolerate the dose level of 80 mg/m^2 was to be discontinued. Dose escalations were not allowed. If the ANC was $< 0.5 \times 10^9$/l and/or platelet count was $< 50 \times 10^9$/l on the day of treatment, the dose of paclitaxel was reduced by two dose levels. In cases of febrile neutropenia, whether or not it was associated with a documented infection and/or severe bleeding, paclitaxel was reduced by three dose levels. The ANC had to be

$\geq 0.5 \times 10^9$/l and the platelet count $\geq 100 \times 10^9$/l prior to the beginning of the next treatment cycle. A maximum delay of 2 weeks was allowed. If hematologic recovery was not achieved, the patient was withdrawn from the study. In case of grade 3 mucositis, the dose of paclitaxel was reduced by one dose level and the dose of PLD by 25%. In patients who developed grade 4 neurotoxicity, severe hypersensitivity reactions, symptomatic arrhythmias or atrioventricular block (except first degree), treatment was discontinued and the patient was removed from the study.

Pharmacokinetic sampling and assay

Pharmacokinetic analyses were performed on 10 patients during the first day of the administration of the combination. Five patients were randomized to receive paclitaxel at a dose of 175 mg/m^2 (3-h infusion), followed immediately by PLD at a dose of 45 mg/m^2 (1-h infusion; PAC/PLD) and five patients received the drugs in the opposite sequence (PLD/PAC). The purpose of this design was to determine the possible effect of either drug on the pharmacokinetics of the other drug.

Blood samples were collected in heparinised tubes for PLD and paclitaxel plasma levels at the following time intervals: pretreatment, 0.25, 1, 2, 3, 4, 8, 12, 24, 48, 96 and 144 h after the start of the infusion of the first drug. Following centrifugation, plasma was removed and stored at –70°C until analysis. All PLD and paclitaxel plasma concentrations were determined by high-performance liquid chromatography (HPLC) [20,21].

Chromatography for paclitaxel was performed using a Jasco 880-PU HPLC pump (Jasco, Japan) and a Marathon-XT autosampler (Spark, The Netherlands). Detection was set at 227 nm with a Fasma 525 programmable detector, model 205UV/Vis (Linear Instruments, San Jose, CA). An octyl 5-µm column (250 × 4.6 mm ID, Alltech Associates, Deerfield, IL) was used. Chromatograms were recorded on a Ezchrom Chromatography Data System laboratory automation computer system (Scientific Software) for peak integration and quantitation.

The HPLC mobile phase for paclitaxel was prepared by mixing 20 ml of 1.0 M ammonium acetate (pH 5.0) with 980 ml of deionized water, 200 ml of methanol and 800 ml of acetonitrile. The resulting mixture was filtered through a 0.22-µm Durapore filter (Millipore, Milford, MA). The flow rate was 1.0 ml/min and the retention time of paclitaxel was 9 min.

Dichloromethane (3 ml) was added to patient plasma samples (1 ml) for extraction. Extraction was accomplished by vigorous shaking for 2 min. The mixture was then centrifuged for 2 min at 150 *g* to separate the lipid and aqueous layers after which the dichloromethane was withdrawn, placed in glass tubes, dried to completion under nitrogen at room temperature and resolubilized with 100 µl of mobile phase.

For PLD analysis blood samples were processed for plasma, centrifuged at 2500 *g* for 10 min at 4°C and stored deep-frozen at approximately –20°C until analyzed. A reversed-phase HPLC assay developed by Gabizon was used to quantify doxorubicin, the active component of PLD. In brief, a 0.4-ml aliquot of plasma was prepared for analysis by adding 0.4 ml isopropanol, 0.4 ml chloroform, 0.5 g ammonium sulfate and internal standard (daunorubicin). The resulting mixture was centrifuged for 15 min at 10 000 r.p.m., and the supernatant solution was decanted and evaporated to dryness under nitrogen at 30°C and the samples were stored dry at –20°C.

For analysis, the concentrated samples were reconstituted in 200 ml isopropanol and were injected at ambient temperature on a HPLC System. The system was a Shimadzu LC-10AD HPLC unit equipped with the RF-10Axl fluorescence detector (Shimadzu, Kyoto, Japan), and a reverse-phase column (LiChrospher RP-8, 5 mm; Agilent Technologies, Palo Alto, C) measuring 150 × 4.6 mm. The mobile phase was an acetonitrile:water (**4**:6 v/v) mixture adjusted to 2.60 pH with perchloric acid. Doxorubicin was detected by fluorescence at 470 nm excitation and 590 nm emission wavelengths, and data processed on a PC/HP Vectra 486/33 VL equipped with a LC-Workstation and class-LC10 software (Kyoto, Japan). All recorded values were based on internal standard.

The linear range of the assay was established between 0.10 and 7.50 mg/ml, with a lower limit of quantitation of 0.05 mg/ml. The within-day coefficient of variation was less than 9% and the overall deviation from nominal values was less than 8%.

The post-infusion paclitaxel kinetics were described using a three-compartment model, according to the following multiexponential equation: $C_p(t) = Ae^{-\alpha t} + Be^{-\beta t} + C^{-\gamma t}$, where C_p is the plasma drug's concentration at time t; A, B and C are hybrids constants, and α, β and γ are the apparent first-order elimination rate constants [22,23]. The half-lives ($t_{1/2}$) were calculated from the equations: $t_{1/2\alpha} = 0.693/\alpha$, $t_{1/2\beta} = 0.693/\beta$ and $t_{1/2\gamma} = 0.693/\gamma$. Other pharmacokinetic parameters were calculated by non-compartmental analysis [24].

The total area under the curve ($AUC_{0-\infty}$) was calculated using the linear trapezoidal method with extrapolation of the terminal phase to infinity (C_{last}/γ) in which C_{last} is the last measured concentration. The area under the moment curve ($AUMC_{0-\infty}$) was also calculated by the trapezoidal rule with extrapolation to infinity ($[C_{last} \times t_{last}]/\gamma + C_{last}/\gamma^2$). Total body clearance (Cl_t) was calculated by dividing

the dose by ($AUC_{0-\infty}$). Volume of distribution at steady state (V_{Dss}) was calculated with the equation: $V_{Dss} = ([D \times AUMC/AUC^2] - [D \times T]/2 \times AUC)$, where T is the infusion time. Peak plasma concentrations (C_{max}) are measured values.

The post-infusion PLD kinetics were analyzed according to an open-two compartment model using the equation $C_p(t) = Ae^{-\alpha t} + Be^{-\beta t}$. The following pharmacokinetic parameters for PLD were determined: C_{max}, ($AUC_{0-\infty}$), K_{el}, which is the elimination rate constant obtained by linear regression on a minimum of three concentrations in the elimination phase (known today as second distribution phase), $t_{1/2\beta}$, Cl_t and V_{Dss} [25].

Phase II study

Toxicity evaluation and response criteria

Drug-induced toxicity was classified in accordance with the ECOG common toxicity criteria (CTC) [26] and standard WHO criteria were used for evaluation of tumor response [27].

Every 3 cycles, response was determined by CT or MRI scans. For disease measurable by physical examination, response was assessed after each course of treatment. All imaging material pertinent to tumor response to chemotherapy was scanned (Mirage II, maximum resolution 9800 × 9800 d.p.i.; UMAX Data Systems, Hsinchu, Taiwan) and evaluated after completion of the study by one of the investigators (A.K.F.).

Statistical analysis

The primary endpoint of the phase II study was to evaluate the response of chemotherapy. The expected overall response rate was assumed to be no more than 35%. A sample size of 49 patients was required to obtain 95% exact confidence limits of 22–50%. The duration of response was calculated in the case of a complete response from the date when the complete response was documented until the date of progression and in the case of a partial response from the initiation of chemotherapy until the date of progression. Time to disease progression (TTP) was calculated from the randomization date to the date progression of the disease was firstly documented (patients who discontinued their treatment for any reason or probably died from disease-related causes were considered at that time, as having disease progression) and survival from the randomization date to the date of last contact or to the date of death. Analysis was conducted on an 'intent-to-treat basis'.

Survival curves were computed by the Kaplan–Meier method and the log-rank test was used for statistical inference [28].

Results

Between October 1998 and December 1999, a total of 60 patients were accrued to the study. Eleven patients enrolled in the phase I trial and 49 patients enrolled in the phase II trial.

Phase I study

Pharmacokinetics

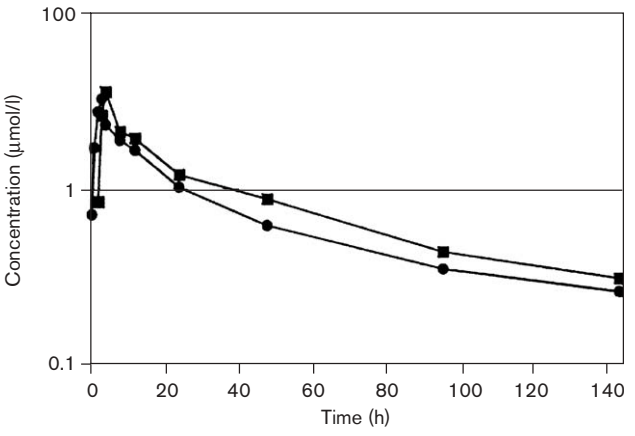
Ten patients entered the pharmacokinetic study and received either paclitaxel followed by PLD (PAC/PLD; five patients) or PLD followed by paclitaxel (PLD/PAC; five patients). The paclitaxel plasma concentrations were slightly higher for all sampling times in patients who received paclitaxel after the PLD infusion (Fig. 1). Similarly, the $AUC_{0-\infty}$ and the $AUMC_{0-\infty}$ of paclitaxel were higher in these patients than those in patients who received paclitaxel before the PLD infusion (median value 110.2 versus 91.8 and 2744.2 versus 1548.1 μmol/l·h, respectively). The other pharmacokinetic parameters of paclitaxel such as elimination half lives ($T_{1/2}$), volume of distribution (V_{Dss}) and total clearance (Cl_t) were similar between the two groups (Table 1).

The PLD plasma concentrations were higher during the distribution phase in the patients receiving the drug after paclitaxel infusion, showing delayed distribution (Fig. 2). There were no other differences in PLD pharmacokinetic parameters in patients who received PLD before or after paclitaxel infusion (Table 2).

PLD dose escalation

No DLT was observed at the first two dose levels (35 and 40 mg/m^2, six patients, 23 cycles; Table 3). No dose reduction or treatment delay was necessary at either dose level. At the third dose level (45 mg/m^2) from a total of five patients (19 cycles), three developed grade 4

Fig. 1

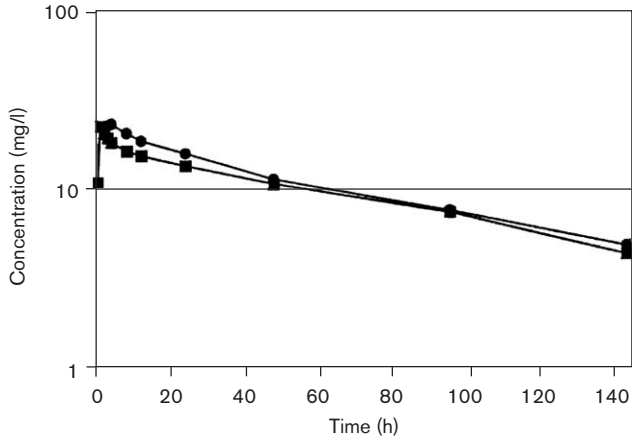


Mean paclitaxel plasma concentrations after a 3-h infusion of 175 mg/m^2 before (PAC/PLD; group A, circles) and after (PLD/PAC; group B, squares) PLD administration.

Table 1 Pharmacokinetic parameters of paclitaxel after a 175 mg/m^2 dose administered during a 3-h infusion provided as a mean value ± SD (median)

	Sequence of infusion PAC/PLD (n=5)	Sequence of infusion PLD/PAC (n=5)
C_{max} (μmol/l)	3.2 ± 0.57 (3.2)	3.5 ± 0.8 (3.49)
$t_{1/2\alpha}$ (h)	3.2 ± 0.74 (3.1)	4.5 ± 1.74 (4.65)
$t_{1/2\beta}$ (h)	27.4 ± 7.42 (29.7)	28.3 ± 10.6 (22.8)
$t_{1/2\gamma}$ (h)	203 ± 68.9 (183.2)	131.7 ± 44.7 (137.1)
$AUC_{0-\infty}$ (μmol/l·h)	85.8 ± 18.8 (91.8)	102.8 ± 17.3 (110.2)
$AUMC_{0-\infty}$ (μmol/l·h)	2404.8 ± 1466.9 (1548.1)	3218.9 ± 1425.3 (2744.2)
V_{Dss} (l)	113.3 ± 52.17 (137.1)	106.8 ± 87.3 (90.4)
Cl_t (l/h)	4.6 ± 1.4 (3.9)	3.2 ± 0.6 (3.2)

Fig. 2



Mean PLD plasma concentration after a 1-h infusion of 45 mg/m^2 before (PLD/PAC; group B, squares) or after (PAC/PLD; group A, circles) paclitaxel administration.

Table 2 Pharmacokinetic parameters of PLD after a 45 mg/m^2 dose administered during a 1-h infusion provided as a mean value ± SD (median)

	Sequence of infusion PAC/PLD (n=5)	Sequence of infusion PLD/PAC (n=5)
C_{max} (mg/l)	23.5 ± 3.1 (24.0)	22.9 ± 2.3 (21.7)
$t_{1/2\beta}$ (h)	68.4 ± 12.8 (63.0)	78.5 ± 28.1 (86.6)
K_{el} (h^{-1})	0.010 ± 0.001 (0.011)	0.010 ± 0.004 (0.008)
$AUC_{0-\infty}$ (mg/l·h)	1324.9 ± 279.4 (1250.0)	1987.5 ± 1020.7 (2045.4)
V_{Dss} (l)	3.41 ± 0.36 (3.30)	2.79 ± 0.58 (2.79)
Cl_t (l/h)	0.035 ± 0.006 (0.036)	0.028 ± 0.014 (0.022)

Table 3 Dose escalation results

Dose level	PLD (mg/m^2)	Paclitaxel (mg/m^2)	Patients (N)	DLT (N)	Toxicity
1	35	175	3	0	–
2	40	175	3	0	–
3	45	175	5	3	febrile neutropenia

neutropenia. Therefore, this dose level was defined as the MTD and the dose immediately below (40 mg/m^2) was selected for the phase II evaluation. During the phase II, PAC was given immediately after the infusion of PLD.

Phase II study

Patient population

Based on the results of the phase I study, 49 patients were treated at dose level 2, and were evaluable for toxicity and response based on an intent-to-treat analysis. Forty-four men and five women with a median age of 62 years (range 38–79) were enrolled (Table 4). The majority of patients had a good performance status (96% performance status 2 or less). In 10 patients, the primary tumor was located in the nasopharynx. The remaining 39 patients had non-nasopharyngeal tumors, the majority of which were located in the larynx, oral cavity and oropharynx. The predominant histology was squamous cell carcinoma (40 patients, 82%). All patients had locoregional assessable disease, with seven patients having metastatic disease only. Seventeen patients (35%) presented with nodal involvement. The most common metastatic sites included the lung and bone. Thirty-seven patients (70%) had prior surgery with or without radiotherapy, four patients had received radiosensitizing chemotherapy, and three patients had received neoadjuvant chemotherapy with cisplatin and 5-FU.

The majority of patients (78%) received between 3 and 6 cycles of the combination for a total of 214 cycles. The median duration between cycles was 28 days (range 24–58) and the median duration of treatment was 20 weeks (range 4–35). Only 7% of the cycles were associated with a delay in treatment mainly because of treatment toxicity.

Of the 214 cycles, 143 (67%) were administered at full dose for both drugs, 149 (70%) at full dose for PLD and 193 (91%) at full dose for paclitaxel. The median relative dose intensity (DI) for PLD was 0.99 (range 0.6–1.18) and the median relative DI for paclitaxel was 0.99 (range 0.55–1.15).

Toxicity

Neutropenia was the most common hematologic toxicity (Table 5). Twenty-two percent of patients developed grade 1 or 2 neutropenia and 26% developed grade 3 or 4 neutropenia. Febrile neutropenia was recorded in 16% of patients, and was managed effectively with parenteral antibiotics and growth factor support. Thrombocytopenia

Table 4 Baseline patient demographics and disease characteristics for phase II

	n	%
N	49	
Age		
median	62	
range	38–79	
Sex		
male	44	90
female	5	10
Performance status		
0	15	31
1	27	55
2	5	10
Unknown	2	4
primary site		
nasopharynx	10	20
oropharynx	9	19
hypopharynx	2	4
larynx	15	31
oral cavity	8	16
paranasal sinuses	2	4
salivary glands	1	2
other	2	4
Histologic type		
SCC	40	82
undifferentiated	4	8
undifferentiated + mucoepidermoid	1	2
other	3	6
unknown	1	2
Extent of disease		
locoregional		
primary	31	63
nodes	17	35
skin	1	2
distant		
lung	9	18
liver	2	4
bone	6	12
other nodes (axillary, mediastinal)	2	4
only locoregional	32	65
only distant	7	15
both	9	18
unknown	1	2
Prior treatment		
no	2	4
surgery	37	80
radiotherapy	29	59
chemotherapy	7	14
unknown	1	2

Table 5 Per patient incidence of toxicity accrued to ECOG CTC

	Grade 1/2 (%)	Grade 3/4 (%)
Anemia	39	4
Neutropenia	22	26
Febrile neutropenia		16
Leukopenia	26	24
Thrombocytopenia	4	
Nausea and vomiting	14	
Allergic reactions	10	
Myalgias/arthralgias	20	
Peripheral neuropathy	31	2
Rash	6	
Stomatitis	26	4
Infection	4	
Fatigue	22	
PPE	12	2

Table 6 Responses (*n*, %) by location of primary tumor

	Nasopharyngeal	Non-nasopharyngeal
CR	1 (10)	–
PR	2 (20)	11 (28)
SD	5 (50)	13 (33)
PD	2 (20)	9 (23)
NE	–	6 (15)
ORR	3 (30)	11 (28)

CR, complete response; PR, partial response; ORR, overall response rate; SD, stable disease; PD, progressive disease; NE, non-evaluable. Values were rounded up. Overall $p=0.284$ (Fisher's exact test) shows no significant difference among the responses between the two groups.

Table 7 Responses (*n*, %) by site of disease

	Locoregional	Distant	h
CR	1 (3)	–	–
PR	10 (31)	3 (43)	–
SD	12 (37.5)	2 (29)	3 (33)
PD	5 (16)	2 (29)	4 (44)
NE	4 (12.5)	–	2 (22)
ORR	11 (34)	3 (43)	–

See Table 6 for abbreviations. Values were rounded up. Overall $p=0.316$ (Fisher's exact test) shows no significant difference among the responses between the three groups.

was mild and never exceeded grade 2, and mild anemia was relatively common (39%). Alopecia was the most frequent non-hematologic toxicity and 55% of patients developed grade 2 alopecia. Only one case of severe (grade 3) palmar–plantar erythrodysesthesia (PPE) was recorded after the third cycle, resulting in treatment delay, but subsiding after treatment discontinuation. Mild stomatitis was recorded in 26% of cases and reached grade 3 in only two patients. There were no renal metabolic toxicities recorded. Nausea and vomiting was mild and easily controlled with standard antiemetics.

Response rate

Of the 49 patients entered, six (all with non-nasopharyngeal tumors) were considered as non-responders based on intent-to-treat analysis. Of these six patients, one died shortly after receiving the first cycle of chemotherapy due to disease progression, three patients withdrew voluntarily from the study after the first course and two patients withdrew due to early treatment-related toxicity [one of them due to severe (grade 3) leukopenia and neurotoxicity, and the other due to severe (grade 4) dermatitis].

The overall response rate for patients with non-nasopharyngeal tumors was 28% with a 95% confidence interval of 15–45% (Table 6). All were partial responses and 13 patients (33%) maintained stable disease as their best response. Response rate among the 10 patients with nasopharyngeal tumors was higher (one with complete response, two with partial response and five with stable disease) than in patients with non-nasopharyngeal tumors. No significant difference was found in response rate in regard to site of disease (Fisher's exact test: $p = 0.316$) (Table 7).

Survival analysis

At the time of median survival assessment there were 44 recorded events (36 due to the underlying disease, four from a cardiac cause, one from a stroke and three from unknown cause). The median survival for the total population was 9.7 months (range 0.13–56 +) and the median time to disease progression was 5.8 months (range 0.13–38.2). Patients with nasopharyngeal tumors did not differ significantly, in terms of survival, compared with those who had non-nasopharyngeal tumors (20.2, 95% CI 2.4–38.0 versus 7.9, 95% CI 5.8–10.0 months, respectively, $p > 0.05$). For the patients who achieved a clinical response, the median duration of response was 8.7 months (range 2.9–46.9 +) and the median time to progression was 5.8 months (range 0.13–38.2). Median duration of response for patients with non-nasopharyngeal tumors was 8.7 months (range 2.9–46.9 +). Among patients with nasopharyngeal tumors, the three responses (one complete and two partial) that were recorded, as previously stated, lasted for 16.8, 14.2 and 7.1 months, respectively. Tumor location was not a predictive factor for time to progression or for response duration ($p > 0.05$ in both cases).

Discussion

With an apparent standstill in response and survival rates, quality of life issues addressing toxicity due to chemotherapy, ease of administration and patient convenience are essential factors to be considered in the design of chemotherapy for this group of patients that is particularly prone to chemotherapy side-effects. The successful introduction of non-platinum couplets in advanced or metastatic non-small cell lung cancer served as a model for this group of patients. The HeCOG has been exploring paclitaxel-based combination chemotherapy for patients with advanced and recurrent HNC over the past decade. Substitution of carboplatin for cisplatin [17,18], the addition of gemcitabine to regimens [11] and the use of taxane-based non-platinum regimens have all been investigated in this patient population. Initial encouraging phase II data with PLD against HNC prompted the group to explore the combination of paclitaxel with PLD [6]. Paclitaxel was used at an intermediate dose of 175 mg/m^2 based on the results from the ECOG randomized study which suggested that no advantage was gained by using high (200 mg/m^2) doses [16].

Paclitaxel demonstrates proven activity against HNC as a single agent with response rates of 20–40% [8–10]. In preclinical studies paclitaxel demonstrates synergy with cisplatin [29]. In a number of phase II trials paclitaxel combined with cisplatin or carboplatin yielded varying response rates between 33 and 62%, depending on the selected patient population, without any substantial improvement in survival [12–19]. The evidence from the literature, however, suggests that the above combination is associated with substantial myelotoxicity. Forastiere *et al.* reported a 70% incidence of grade 3 or 4 neutropenia and an unacceptably high (10%) toxic death rate when combining low-dose or high-dose paclitaxel with cisplatin, despite the use of prophylactic granulocyte macrophage colony stimulating factor (G-CSF) [14]. It was postulated that the excessive toxicity was related to the 24-h infusion of paclitaxel. In another study, however, using paclitaxel at the same high dose of 200 mg/m^2 but at a 3-h infusion rate in combination with carboplatin, Clark *et al.* reported a 38% incidence of grade 3 or 4 leukopenia and an 8% toxic death rate [19]. Clearly the combination of paclitaxel with cisplatin or carboplatin with moderate response rates and excessive toxicity, cannot replace the gold standard of cisplatin with continuous infusion of 5-FU.

From the pharmacological point of view, the interaction between paclitaxel and epirubicin or doxorubicin has been studied previously with some conflicting results [30,31]. However, it is generally accepted that when doxorubicin is infused shortly after paclitaxel, its clearance is slowed down. Because the pharmacokinetic profile of PLD is considerably different from that of conventional doxorubicin, we investigated whether there was a sequence-dependent interaction between PLD and paclitaxel by examining the pharmacokinetics of both drugs. The initial administration of paclitaxel as a 3-h infusion did not appear to affect the kinetic behavior of PLD, except perhaps causing some delay of its distribution resulting in higher concentrations only during the distribution phase.

Conversely, the initial administration of PLD as a 1-h infusion resulted in slightly higher plasma concentrations and higher AUC and AUMC of paclitaxel. This could be explained by the decreased distribution of paclitaxel after the first exposure to the PLD, since the elimination process of paclitaxel was not affected in this study. The sequence of drug administration did not cause clinically significant modifications in pharmacokinetics of both drugs, although an interaction cannot be excluded in view of the limited number of patients studied.

In the present study, prophylactic G-CSF was not used, and the reported rates of neutropenia and febrile neutropenia (26 and 16%, respectively) did not differ from those of other studies. Most importantly there were no deaths from neutropenic sepsis. Therefore this combination and schedule of paclitaxel with PLD does not warrant routine G-CSF use, since neutropenia rates are acceptable by international standards.

Minimizing the incidence of chemotherapy-induced mucositis is of utmost importance in this patient

population with substantial coincident weight loss and dehydration. Prior radiation therapy may exacerbate chemotherapy-induced mucositis; however, it was not common in this study (4%). Using PLD as a single agent in a phase I study in a similar group of patients Caponigro *et al.* reported severe stomatitis in four of 24 patients (16%) treated at dose levels between 40 and 50 mg/m^2 administered in 3-week intervals [6]. These results contrast with the high incidence of grade 3/4 mucositis reported with the cisplatin/5-FU-based regimens; approximately 20% for cisplatin/5-FU and approximately 40% for cisplatin/5-FU/leucovorin [32–34].

Skin toxicity manifested in nearly all cases in the form of PPE, a painful dry desquamating dermatitis, affecting mainly hands and feet. Caponigro *et al.* reported an incidence of grade 1–3 PPE in 58% of patients receiving PLD at 3-week intervals [4]. In the present study, the incidence of all grades of PPE was relatively low (14%), possibly due to a lower dose and longer cycle length (every 4 weeks). It should be noted, however, that two patients withdrew early from the study due to grade 4 dermatitis. As in Caponigro's study, PPE occurred usually after the third cycle and was managed principally by increasing cycle length.

The response rate in the present study is comparable with those reported from other phase II studies. Using the paclitaxel and carboplatin combination, Clark *et al.* reported an overall response rate of 27%, Fountzilas *et al.* a response rate of 20% and Stathopoulos *et al.* a response rate of 39% [17–19]. Dunphy *et al.* reported higher response rates (54%); however, newly diagnosed and previously untreated patients, as well as patients with nasopharyngeal tumors which are highly chemosensitive were included in the study [35]. Using paclitaxel with gemcitabine as a non-platinum alternative, Fountzilas *et al.* reported an overall response rate of 41% with 11% complete responses [11].

A unique aspect of this study was that a novel non-platinum combination was introduced in the management of recurrent and metastatic HNC, and generated response rates which were comparable to other platinum-containing regimens reported in the literature. In addition, the favorable toxicity profile along with its apparent ease of administration on an outpatient basis makes this combination an attractive non-platinum alternative in the management of recurrent and metastatic HNC. Since both PLD and paclitaxel are radiosensitizing agents, their combination could serve as a basis for chemoradiotherapy protocols using re-irradiation in order to augment response rates in locoregionally recurrent HNC [1,36].

References

1 Koukourakis MI, Koukouraki S, Giatromanolaki A, *et al.* Liposomal doxorubicin and conventionally fractionated radiotherapy in the treatment of locally advanced non-small-cell lung cancer and head and neck cancer. *J Clin Oncol* 1999; **17**:3512–3521.

2 Buntzel J, Weinaug R, Glatzel M, *et al.* Pegylated liposomal doxorubicin (CAELYX) in the treatment of advanced head and neck cance—results of a phase I/II study. *Proc Am Soc Clin Oncol* 1999; 1540a.

3 Harrington KJ, Lewanski C, Northcote AD, *et al.* Phase II study of pegylated liposomal doxorubicin (Caelyx) as induction chemotherapy for patients with squamous cell cancer of the head and neck. *Eur J Cancer* 2001; **37**:2015–2022.

4 Rigatos SK, Tsavdaridis D, Athanasiadis A, Stathopoulos JG, Stathopoulos GP. Paclitaxel and liposomal doxorubicin (Caelyx) combination in advanced breast cancer patients: a phase II study. *Oncol Rep* 2003; **10**:1817–1819.

5 Campos SM, Matulonis UA, Penson RT, *et al.* Phase II study of liposomal doxorubicin and weekly paclitaxel for recurrent Mullerian tumors. *Gynecol Oncol* 2003; **90**:610–618.

6 Caponigro F, Comella P, Budillon A, *et al.* phase I study of Caelyx (doxorubicin HCl, pegylated liposomal) in recurrent or metastatic head and neck cancer. *Ann Oncol* 2000; **11**:339–342.

7 Goldspiel BR. Clinical overview of the taxanes. *Pharmacotherapy* 1997; **17**:110S–125S.

8 Loeffler T, Freund W, Lipke J. Schedule and dose intensified paclitaxel as weekly one hour infusion. Evidence for an improved toxicity profile and response activity in pretreated solid tumors. *Proc Am Soc Clin Oncol* 1995; **14**:470.

9 Smith RE, Thornton DE, Allen J. A phase II trial of paclitaxel in squamous cell carcinoma of the head and neck with correlative laboratory studies. *Semin Oncol* 1995; **22**:41–46.

10 Forastiere AA, Shank D, Neuberg D, *et al.* Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group trial (PA390). *Cancer* 1998; **82**:2270–2274.

11 Fountzilas G, Stathopoulos G, Nicolaides C, *et al.* Paclitaxel and gemcitabine in advanced non-nasopharyngeal head and neck cancer: a phase II study conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol* 1999; **10**:475–478.

12 Benasso M, Numico G, Merlano M, *et al.* Phase I–II study of Taxol, cisplatin (CDDP) and fluorouracil (FU) in relapsed squamous cell carcinoma of the head and neck. *Proc Am Soc Clin Oncol* 1997; 1415a.

13 Hussain M, Salwen W, Kucuk O, *et al.* Paclitaxel, cisplatin, and 5-fluorouracil in patients with advanced or recurrent squamous cell carcinoma of the head and neck: a preliminary report. *Semin Oncol* 1997; **24**(**suppl 19**):43–45.

14 Hainsworth JD, Meluch AA, Greco FA. Paclitaxel, carboplatin, and long-term continuous 5-fluorouracil infusion in the treatment of upper aerodigestive malignancies: preliminary results of phase II trial. *Semin Oncol* 1997; **24**(**suppl 19**):38–42.

15 Shin DM, Glisson BS, Khuri FR, *et al.* phase II trial of paclitaxel, ifosfamide, and cisplatin in patients with recurrent head and neck squamous cell carcinoma. *J Clin Oncol* 1998; **16**:1325–1330.

16 Forastiere AA, Leong T, Rowinsky E, *et al.* phase III comparison of high-dose paclitaxel + cisplatin + granulocyte colony-stimulating factor versus low-dose paclitaxel + cisplatin in advanced head and neck cancer: Eastern Cooperative Oncology Group Study E1393. *J Clin Oncol* 2001; **19**: 1088–1095.

17 Fountzilas G, Skarlos D, Athanassiades A, *et al.* Paclitaxel by three-hour infusion and carboplatin in advanced carcinoma of nasopharynx and other sites of the head and neck. A phase II study conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol* 1997; **8**:451–415.

18 Stathopoulos GP, Rigatos S, Papakostas P, *et al.* Effectiveness of paclitaxel and carboplatin combination in heavily pretreated patients with head and neck cancers. *Eur J Cancer* 1997; **33**:1780–1783.

19 Clark JI, Hofmeister C, Choudhury A, *et al.* phase II evaluation of paclitaxel in combination with carboplatin in advanced head and neck carcinoma. *Cancer* 2001; **92**:2334–2340.

20 Willey TA, Bekos EJ, Gaver RC, *et al.* High-performance liquid chromatographic procedure for the quantitative determination of paclitaxel (Taxol) in human plasma. *J Chromatogr* 1993; **621**:231–238.

21 Gabizon AA, Barenholz Y, Bialer M. Prolongation of the circulation time of doxorubicin encapsulated in liposomes containing a polyethylene glycol-derivatized phospholipid: pharmacokinetic studies in rodents and dogs. *Pharm Res* 1993; **10**:703–708.

22 Huizing MT, Keung AC, Rosing H, *et al.* Pharmacokinetics of paclitaxel and metabolites in a randomized comparative study in platinum-pretreated ovarian cancer patients. *J Clin Oncol* 1993; **11**:2127–2135.

23 Coukell AJ, Spencer CM. Polyethylene glycol-liposomal doxorubicin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the management of AIDS-related Kaposi's sarcoma. *Drugs* 51997; **3**:520–538.
24 Gibaldi M. *Biopharmaceutics and Clinical Pharmacokinetics*. Philadelphia, PA: Lea & Febiger; 1984.
25 Gibaldi M, Perier D. *Pharmacokinetics*. New York: Marcel Dekker; 1990.
26 *Common Toxicity Criteria*, 2nd edn. Bethesda. MD: Cancer Therapy Evaluation Program, National Cancer Institute; 1999.
27 WHO. *Handbook for Reporting Results of Cancer Treatment*. WHO Offset Publication 48. Geneva: WHO; 1972.
28 Peto R, Peto J. Asymptomatically efficient rank invariant test procedures [with Discussion]. *J R Stat Soc* 1972; **135**:185–206.
29 Parker R, Lee K, Dabholkar M. Influence of Taxol: cisplatin sequencing on cisplatin-DNA adduct repair in human ovarian cancer cells. *Proc Am Ass Cancer Res* 1993; **34**:356.
30 Venturini M, Lunardi G, Del Mastro L, *et al*. Sequence effect of epirubicin and paclitaxel treatment on pharmacokinetics and toxicity. *J Clin Oncol* 2000; **18**:2116–2125.
31 Holmes FA, Madden T, Newman RA, *et al*. Sequence-dependent alteration of doxorubicin pharmacokinetics by paclitaxel in a phase I study of paclitaxel and doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* 1996; **14**:2713–2721.
32 Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. *N Engl J Med* 1993; **328**:184–194.
33 Schantz S, Harrison L, Forastiere A. Tumors of the nasal cavity and paranasal sinuses, nasopharynx, oral cavity, and oropharynx. In: DeVita V, Hellman S, Rosenberg S (editors): *Cancer: Principles and Practice of Oncology*, 5th edn. Philadelphia, PA: Lippincott-Raven; 1997, pp. 741–801;
34 Papadimitrakopoulou VA, Dimery IW, Lee JJ, *et al*. Cisplatin, fluorouracil, and l-leucovorin induction chemotherapy for locally advanced head and neck cancer: the MD Anderson Cancer Center experience. *Cancer J Sci Am* 1997; **3**:92–99.
35 Dunphy F, Boyd J, Dunleavy T. Paclitaxel and carboplatin in head and neck cancer. *Semin Oncol* 1997; **24**(**suppl 19**):25–27.
36 Leonard CE, Chan DC, Chou TC, *et al*. Paclitaxel enhances *in vitro* radiosensitivity of squamous cell carcinoma cell lines of the head and neck. *Cancer Res* 1996; **56**:5198–5204.