

Phase I and Pharmacokinetic Study of Genexol-PM, a Cremophor-Free, Polymeric Micelle-Formulated Paclitaxel, in Patients with Advanced Malignancies

Tae-You Kim,¹ Dong-Wan Kim,¹
Jae-Yong Chung,² Sang Goo Shin,²
Sung-Chul Kim,³ Dae Seog Heo,¹
Noe Kyeong Kim,¹ and Yung-Jue Bang¹

¹Department of Internal Medicine, and ²Department of Pharmacology and Clinical Pharmacology Unit, Seoul National University College of Medicine, Seoul, Korea, and ³Samyang Research Corporation, Salt Lake City, Utah

ABSTRACT

Purpose: The rationale for developing an alternative paclitaxel formulation concerns Cremophor EL-related side effects, and a novel paclitaxel delivery system might augment its therapeutic efficacy. Genexol-PM is a polymeric micelle formulated paclitaxel free of Cremophor EL. A phase I study was performed to determine the maximum tolerated dosage, dose-limiting toxicities, and the pharmacokinetic profile of Genexol-PM in patients with advanced, refractory malignancies.

Experimental Design: Twenty-one patients were entered into the study. Genexol-PM was i.v. administered over 3 h every 3 weeks without premedication. The Genexol-PM dose was escalated from 135 mg/m² to 390 mg/m².

Results: All of the patients were evaluable for toxicity and response. Acute hypersensitivity reactions were not observed. Neuropathy and myalgia were the most common toxicities. During cycle 1, grade 3 myalgia occurred in 1 patient at 230 and 300 mg/m², respectively. At 390 mg/m², 2 of 3 patients developed grade 4 neutropenia or grade 3 polyneuropathy. Therefore, the maximum tolerated dosage was determined to be 390 mg/m². There were 3 partial responses (14%) among the 21 patients. Of the 3 responders, 2 were refractory to prior taxane therapy. The paclitaxel area under the curve from time 0 to infinity and peak or maximum paclitaxel concentration seemed to increase with escalating dose, except at 230 mg/m², which suggests that Genexol-PM has linear pharmacokinetics.

Conclusion: The main dose-limiting toxicities were neuropathy, myalgia, and neutropenia, and the recommended dosage for a phase II study is 300 mg/m². Genexol-PM is believed to be superior to conventional paclitaxel in terms of the obviation of premedication and the delivery of higher paclitaxel doses without additional toxicity.

INTRODUCTION

Paclitaxel (Taxol; Bristol-Myers Squibb, Wallingford, CT) is an anticancer agent effective for the treatment of breast, ovarian, lung, and head and neck cancers (1). Its dose-response aspects are controversial, and higher doses have been limited by neuropathy and neutropenia (2). Dose-limiting toxicities (DLTs) by paclitaxel may be related with the taxane itself or with the vehicle required to formulate the drug. Because of water insolubility, paclitaxel is formulated with the micelle-forming vehicle Cremophor EL (CrEL) to enhance drug solubility (3). However, the addition of CrEL has been shown to cause hypersensitivity reaction (HSR) and neuropathy (1–3). In addition, CrEL significantly alters the pharmacokinetics of paclitaxel (2–5). The pharmacokinetic behavior of paclitaxel has been proposed to be distinctly nonlinear because the drug is trapped in micelles, making it less available for tissue distribution, metabolism, and biliary excretion, whereas CrEL-free paclitaxel appears to be linear (6, 7). Moreover, paclitaxel must be prepared in either a glass bottle or in non-polyvinyl chloride infusion systems with in-line filtration to prevent precipitation from CrEL and solvent (8). On the other hand, CrEL may positively affect the cytotoxic effect of paclitaxel. It has been proposed to induce a cell cycle block distinct from that seen with paclitaxel (9) or to reverse the multidrug resistance phenotype (10, 11). However, it is uncertain whether the plasma concentration of CrEL attainable during Taxol infusion is relevant in solid tumors (4, 12, 13). Collectively, the addition of CrEL is closely related with toxicity, inconvenience, less effective biodistribution, and special devices for the administration of paclitaxel.

Therefore, to circumvent these unfavorable effects resulting from the addition of CrEL, efforts have been made to develop new taxane formulations that do not require CrEL as a solubilizer. Several drug delivery systems using emulsion, micelles, water-soluble prodrugs, and conjugates are currently under clinical investigation (14–19). For example, ABI-007, which is a CrEL-free, protein stabilized, nanoparticle paclitaxel formulation, was safely administered without HSRs up to 300 mg/m² (20). A new polymer-conjugated derivative of paclitaxel, PNU166945, displayed linear pharmacokinetic behavior for the bound fraction as well as for released paclitaxel (21). Among the various alternatives for CrEL, the polymeric micelles have a great potential in terms of water solubility, *in vivo* stability, and the nanoscopic size of the micellar structure. Moreover, this

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Requests for reprints: Tae-You Kim, Department of Internal Medicine, Seoul National University College of Medicine, 28, Yongon-dong, Chongno-gu, Seoul, 110-744, Korea. Phone: 82-2-760-2390; Fax: 82-2-762-9662; E-mail: bangyj@plaza.snu.ac.kr.

A Structure of amphiphilic block copolymer

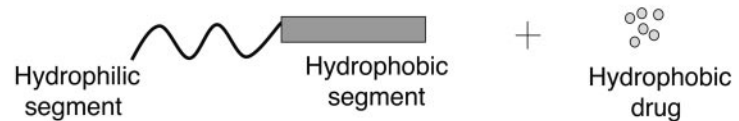
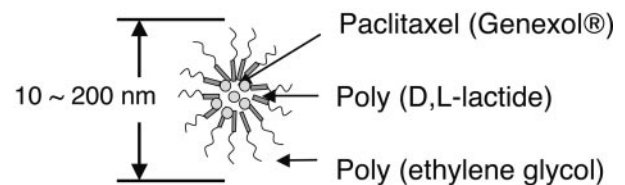


Fig. 1 Formulation of polymeric micelle loaded Genexol-PM.

B Polymeric micelle formulated paclitaxel (Genexol-PM)



novel delivery system has been shown to be effective in targeting the therapeutics to their site of action (22–25). The polymeric micelles are composed of hundreds of amphiphilic diblock copolymers and have a diameter of 20–50 nm. Block copolymers include poly-(ethylene glycol), which is useful for nonimmunogenic carriers, and biodegradable core-forming poly-(D,L-lactic acid) required for the solubilization of the hydrophobic drug. Samyang Corporation (Seoul, Korea) has developed a novel taxane formulation, Genexol-PM, which is a polymeric micelle loaded paclitaxel without CrEL (Fig. 1). Genexol-PM was found to have a three-times higher maximum-tolerated dose (MTD) in nude mice, and the biodistribution of Genexol-PM showed 2–3-folds higher levels in various tissues including, liver, spleen, kidney, and lung, and more importantly in tumors. The *in vivo* antitumor efficacy of Genexol-PM was also significantly greater than that of Taxol (26). On the basis of these promising results, we performed a phase I study to determine the MTD, DLTs, and the pharmacokinetic profile of Genexol-PM in patients with advanced, refractory malignancies.

PATIENTS AND METHODS

Eligibility. This study was performed at the Seoul National University Hospital (Seoul, Korea). Patients were considered eligible if they had histological evidence of advanced solid malignancies refractory to conventional treatment or for whom no effective therapy existed. The inclusion criteria included the following: (a) age of 19–70 years; (b) an Eastern Cooperative Oncology Group performance status of 2 or less; (c) a life expectancy of at least 3 months; (d) adequate hematological, renal, and hepatic function; and (e) no prior chemotherapy, immunotherapy, or radiation therapy for a period of 4 weeks. Patients with the following conditions were excluded: (a) active bacterial infection requiring antibiotic-treatment; (b) the presence of psychiatric disease, brain metastasis, or seizure disorder; and (c) pregnant or lactating women. All of the patients gave written informed consent according to national and institutional guideline before therapy.

Study Design. This study was an open-label phase I, dose-escalation study. Samyang Corporation supplied the Genexol-PM. One vial of Genexol-PM contains 30 mg of paclitaxel

(Genexol) and 150 mg of methoxy polyethylene glycol-poly (D,L-lactide) as a solubilizer (26). Five-ml saline solution for injection was aseptically transferred to the vial containing Genexol-PM. Each 1 ml of diluted solution contained 6 mg of paclitaxel and 30 mg of methoxy polyethylene glycol-poly (D,L-lactide). After brief stirring, clear colorless solution was additionally diluted in 500 ml of 5% dextrose at final concentrations of 0.6–3.0 mg/ml and considered to be stable for at least 12 h at room temperature. Because there is neither the leaching of the plasticizer from polyvinyl chloride equipment nor the precipitation of paclitaxel crystal, it can be safely administered using conventional polyvinyl chloride infusion set without in-line filtration. The Genexol-PM was administered *i.v.* in an outpatient setting into a peripheral vein for 3 h once every 3 weeks. All of the treatments were administered without premedication.

Toxicity was graded according to the National Cancer Research Institute Common Toxicity Criteria. The DLT was defined as a National Cancer Research Institute Common Toxicity Criteria grade 3 or 4 nonhematologic toxicity (except for nausea, vomiting, and alopecia), grade 4 neutropenia, or grade 4 thrombocytopenia that occurred during the first cycle of treatment. Dose escalation followed the standard “3 + 3” rule. Cohorts of 3 patients were treated with increasing Genexol-PM doses, which were started at 135 mg/m², which was equivalent to one tenth of the LD₁₀ in mice (1302 mg/m²; Ref. 26). The dose was increased in 30% increments in a group of 3 patients, provided that none of these patients experienced DLT. If 1 of these 3 patients experienced DLT, 3 additional patients were entered at that dose level. If no DLT was observed in this second group of 3, the dose was escalated to next higher dose level. When 2 or more of the first 3 patients experienced DLT, a total of 6 patients should be treated at the one dose level below. The MTD was defined as one dose level higher at which none or 1 of 6 patients develops DLT or as current dose level at which 2 or more of 6 patients develop DLT.

An evaluation of the treatment efficacy was performed at the end of treatment, and responses were assessed using WHO response criteria. Treatment efficacy was defined as the best tumor response during treatment. Treatment was stopped either

if the disease progressed, if grade 4 toxicity occurred, if the performance status of the patients was Eastern Cooperative Oncology Group 4, or if a patient refused additional treatment.

Pharmacokinetic Study. At least 2 patients per dose level underwent blood sampling during the administration of the first Genexol-PM cycle. The drug was administered by continuous infusion over 3 h. Blood samples (5 ml) were collected in heparinized tubes before infusion and at 1.5 h into infusion, and 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 24, 34, and 48 h after infusion. Plasma was separated immediately by centrifugation ($1500 \times g$, 10 min), and stored at -20°C until analysis. The paclitaxel concentrations in plasma were determined by reverse-phase high-performance liquid chromatography with a UV detector. Samples were extracted with ethyl acetate and mixed with acetonitrile as a mobile phase for high-performance liquid chromatography analysis. The pharmacokinetic parameters of the paclitaxel after Genexol-PM administration were estimated by using the noncompartmental open model and the WinNonlin program (version 3.1; Pharaight Corp., Mountain View, CA). The peak or maximum paclitaxel concentration (C_{max}) and the corresponding peak time were the values observed. The elimination half-life ($T_{1/2}$) was determined by $\ln(2)/\lambda_z$ derived from the linear regression analysis of the terminal phase. The area under the curve (AUC) from time 0 to infinity (AUC_{inf}) was obtained by summing AUC_{last} and AUC_{ext} . The dose area relationship (total dose divided by AUC_{inf}) was used to determine total body clearance. The volume of the distribution was determined based on the terminal phase. Descriptive statistics were computed for pharmacokinetic assessment. Regression analysis of AUC_{inf} versus dose was performed to gain an appreciation of pharmacokinetic linearity, if evident, for the dose range evaluated in this trial. Differences between the C_{max} and AUC_{inf} means, according to dose level or the presence of neuromuscular toxicity, were analyzed for significance using the ANOVA *t* test.

Table 1 Patient characteristics

| | |
|--------------------|----------------------|
| No. of patients | 21 |
| Sex | |
| Male/female | 15/6 |
| Age | |
| Median (range) | 52 (27–63 years old) |
| ECOG ^a | |
| 0–1 | 21 |
| Tumor type | |
| Lung | 8 |
| Colorectal | 2 |
| Renal cell | 2 |
| Breast | 1 |
| Ovary | 1 |
| Esophagus | 1 |
| Others | 6 |
| Prior chemotherapy | 21 |
| <3 regimens | 9 |
| ≥ 3 regimens | 12 |
| Prior taxane | 9 |
| <6 months | 6 |
| ≥ 6 months | 3 |

^a ECOG, Eastern Cooperative Oncology Group.

Table 2 Dosage escalation scheme of Genexol-PM

| Level | Paclitaxel dose (mg/m ²) | No. of patients | Total cycles | No. of patients with DLT ^a |
|-------|--------------------------------------|-----------------|--------------|---------------------------------------|
| 1 | 135 | 3 | 24 | 0 |
| 2 | 175 | 3 | 15 | 0 |
| 3 | 230 | 6 | 16 | 1 |
| 4 | 300 | 6 | 16 | 1 |
| 5 | 390 | 3 | 10 | 2 |

^a DLT, dose-limiting toxicity.

RESULTS

Twenty-one patients were entered into this study between August 2001 and October 2002, and all were eligible for analysis. Patient characteristics are listed in Table 1. The median patient age was 52 years (range, 27–63). Fifteen patients were male and 6 female. Eight patients had lung cancer, 2 colorectal cancer, 2 renal cell cancer, and 9 cancers, including ovarian and breast cancer. All of the patients received prior chemotherapy, and 12 received 3 or more types of chemotherapeutic regimens. Nine patients had received prior taxane therapy, and 6 of these showed tumor progression within 6 months of the last taxane. A total of 81 cycles of Genexol-PM was administered with a median of 3.9 cycles per patient (range, 1–5).

Determination of MTD and DLTs. The dose-escalation scheme of Genexol-PM is listed in Table 2. All of the treatments were administered without premedicating hydrocortisone and histamine blocker. No hypersensitivity reaction was observed in any patient. Because grade 3 or greater toxicity did not develop at dose level 1 (135 mg/m²) or 2 (175 mg/m²), the escalation proceeded to dose level 3. At dose level 3 (230 mg/m²), 1 of the first 3 patients developed grade 3 myalgia. Three more patients were accrued at this dose level with no additional instances of grade 3 or 4 toxicity. At dose level 4 (300 mg/m²), 1 of the first 3 patients also experienced grade 3 myalgia. An additional 3 patients were accrued at level 4, and no DLT was observed in these patients. At dose level 5 (390 mg/m²), 2 of the first 3 patients developed grade 3 sensory and motor neuropathy, and grade 4 neutropenia, respectively. Because 2 of the first 3 patients experienced DLTs at dose level 5, and 1 of 6 patients developed DLT at dose level 4, dose level 5 was defined as the MTD. Thus, the MTD of Genexol-PM administered as a 3-h infusion every 3 weeks was 390 mg/m². The DLTs were myalgia, sensory and motor neuropathy, and neutropenia.

Hematological Toxicity. Table 3 summarizes the drug-related hematological toxicities observed during the study. Grade 3 neutropenia occurred in 1 patient at dose levels 3 and 4, respectively. Grade 4 neutropenia was observed at dose level 5 in a patient who had refractory small cell lung cancer and had been previously heavily pretreated with etoposide, cisplatin, topotecan, gemcitabine, and carboplatin. However, no patient with grade 3 or 4 neutropenia experienced any related complications such as fever. Because the neutrophil count recovered by day 21, treatment delay or growth factor support due to neutropenia was never required.

Nonhematological Toxicity. Tables 4 and 5 summarize the drug-related nonhematological toxicities observed during

Table 3 Hematologic toxicities^a

| Dose level | No. of patients/cycles | Anemia | | | | Neutropenia | | | | Thrombocytopenia | | | |
|------------|------------------------|--------|----|----|----|-------------|----|----|----|------------------|----|----|----|
| | | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| 1 | 3/24 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 2 | 3/15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 6/16 | 1 | 5 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| 4 | 6/16 | 9 | 1 | 0 | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 0 | 0 |
| 5 | 3/10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

^a Expressed as the number of cycles with indicated side effects during the treatments.

Table 4 Neuromuscular toxicities^a

| Dose level | No. of patients/cycles | Neuropathy-motor | | | | Neuropathy-sensory | | | | Myalgia | | | |
|------------|------------------------|------------------|----|----|----|--------------------|----|----|----|---------|----|----|----|
| | | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| 1 | 3/24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 2 | 3/15 | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 4 | 0 | 0 | 0 |
| 3 | 6/16 | 0 | 1 | 0 | 0 | 3 | 5 | 0 | 0 | 6 | 3 | 1 | 0 |
| 4 | 6/16 | 0 | 0 | 0 | 0 | 6 | 4 | 0 | 0 | 6 | 9 | 1 | 0 |
| 5 | 3/10 | 0 | 0 | 1 | 0 | 1 | 6 | 2 | 0 | 10 | 0 | 0 | 0 |

^a Expressed as the number of cycles with indicated side effects during the treatments.

the treatments. The most common nonhematological effects of Genexol-PM were neuromuscular toxicities. Almost all of the patients developed sensory neurotoxicity, characterized by stocking/glove distribution, numbness, and pain at the extremities. Every patient had a past history of cisplatin administration and complained of mild paresthesia after the first cycle of Genexol-PM. At dose level 5, 1 patient who had non-small cell lung cancer complained of severe sensory polyneuropathy after the second cycle of chemotherapy. The patient also developed motor weakness of the lower extremities. Nerve conduction studies and electromyography were shown to be consistent with polyneuropathy. Because of grade 4 toxicity, the patient was taken off treatment, and thereafter, his neurological symptoms improved. All of the patients at dose levels 3 and 4 developed grade 3 myalgia. Muscle ache developed during the first week after the treatment. Because of pain, the patients required analgesics, and their daily activities were disrupted. The onset of myalgia, which typically involved both upper and lower extremities, occurred 3–5 days after infusion, but symp-

tomatic improvement was always observed between days 8 and 21 in most patients. The myalgia was controlled by nonsteroidal anti-inflammatory drugs from the second cycle. Other minor toxicities included alopecia, skin changes, and nausea. Alopecia was universal. Skin toxicity including pruritus and urticaria was also mild. Gastrointestinal complication such as nausea, anorexia, and diarrhea were also mild and transient.

Antitumor Response. All of the patients had measurable sites that were evaluable for antitumor response. Partial responses were observed in 3 of the 21 patients (14%), 2 of whom had prior exposure to taxane. The first patient with non-small cell lung cancer, entered at dose level 2 (175 mg/m²), did not show an objective response to previous chemotherapy with paclitaxel and carboplatin. This patient experienced a 77% decrease in the size of lung metastasis. This response lasted for 6.5 months. The second patient with taxane-refractory ovarian cancer at dose level 3 (230 mg/m²) had received five prior chemotherapy regimens consisting of cyclophosphamide/cisplatin, paclitaxel/carboplatin, single agent topotecan, paclitaxel, and

Table 5 Other nonhematologic toxicities^a

| Toxicity | Level 1 (24 cycles) | | Level 2 (15 cycles) | | Level 3 (16 cycles) | | Level 4 (16 cycles) | | Level 5 (10 cycles) | |
|----------|---------------------|------|---------------------|------|---------------------|------|---------------------|------|---------------------|------|
| | G1–2 | G3–4 | G1–2 | G3–4 | G1–2 | G3–4 | G1–2 | G3–4 | G1–2 | G3–4 |
| Alopecia | 15 | 2 | 9 | 6 | 4 | 5 | 11 | 0 | 3 | 0 |
| Skin | 0 | 0 | 10 | 4 | 5 | 0 | 1 | 0 | 1 | 0 |
| Nausea | 5 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| Anorexia | 1 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 |
| Diarrhea | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 |
| Cough | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Dyspnea | 1 | 0 | 6 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Hepatic | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Renal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

^a Expressed as the number of cycles with indicated side effects during the treatments.

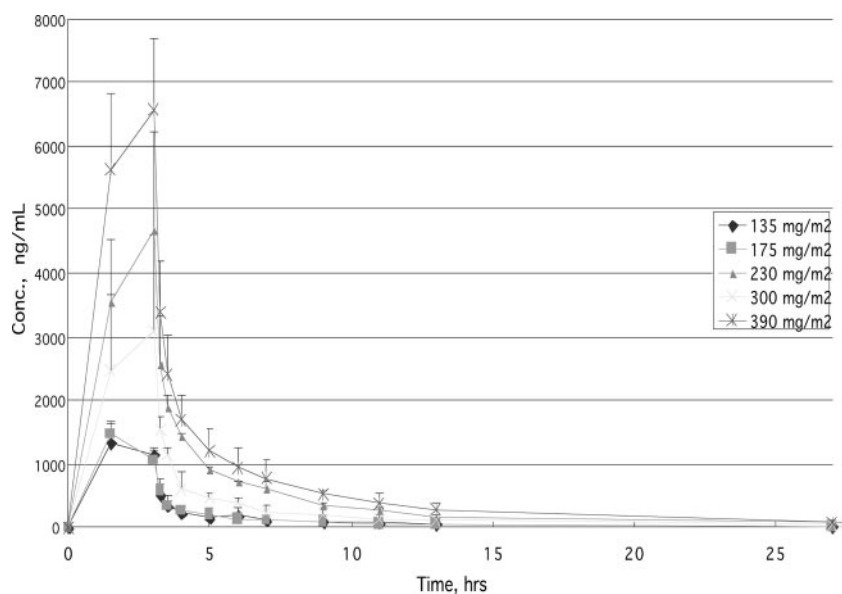


Fig. 2 Plasma concentration-time profile of Genexol-PM.

docetaxel. This patient showed a significant improvement in peritoneal carcinomatosis, and the response was durable for 3.7 months. The third patient at dose level 5 (390 mg/m²), who had refractory small cell lung cancer, was taxane-naïve. This patient showed an 84% decrease in lung mass and mediastinal lymph nodes and showed partial response until the last sixth cycles of chemotherapy. However, disease progression was noted 6.3 months after the response. Six patients (28%) remained stable, whereas 12 patients showed disease progression.

Pharmacokinetics. Pharmacokinetic evaluations were performed in 13 patients over the 135–390 mg/m² dose range. The profiles of 2 patients were not included in the analysis because the data showed unexpectedly low paclitaxel concentrations. Fig. 2 shows the concentration *versus* time curves of paclitaxel at each Genexol-PM dose level. Plasma concentrations peaked between 1.5 and 3.32 h of the infusion, and the decline from C_{max} was biphasic. The pharmacokinetic parameters of the total paclitaxel after Genexol-PM administration are summarized in Table 6. Both the AUC_{inf} and C_{max} for total paclitaxel increased proportionally with increasing dose, except at dose level 3 (Fig. 3). The pharmacokinetics of Genexol-PM administered for 3 h appeared to be nonlinear across the whole dose range. Calculations from the data in Fig. 3 revealed a 5-fold increase in the AUC_{inf} and a 4-fold increase in C_{max} over a 3-fold increase in dose from 135 mg/m² to 390 mg/m². The coefficients of AUC_{inf} and C_{max} variation were <0%, except at

230 mg/m². However, excluding 230 mg/m², the pharmacokinetics of Genexol-PM appeared to be linear (Fig. 4). The AUC_{inf} and C_{max} of Genexol-PM revealed lower values than equivalent doses of Taxol (data not shown). The terminal plasma T_{1/2} of total paclitaxel after Genexol-PM administration (135–300 mg/m²) ranged from 11.0 to 12.7-h and did not show any significant dose-dependent changes except in the 390 mg/m² group. The T_{1/2} of Genexol-PM is relatively short, compared with the 20.1 h of Taxol (Table 6; Ref. 27). It has been reported that CrEL inhibits the metabolism of paclitaxel in the rat. Thus, the metabolism of CrEL-free Genexol-PM may be augmented compared with Taxol, and this would result in lower values of AUC_{inf} and T_{1/2}. Fig. 5 is a plot that depicts the relationship between AUC_{inf} and C_{max} *versus* the neuromuscular toxicities for each group of patients who experienced grade 3–4 toxicity and who did not. The development of grade 3–4 neuropathy or myalgia seemed to be correlated with pharmacokinetic parameters but did not show statistically significant different AUC_{inf} ($P = 0.2281$) and C_{max} ($P = 0.3363$) values between two groups of patients.

DISCUSSION

The paclitaxel vehicle CrEL has been shown to influence the toxicity, pharmacokinetics, and antitumor activity of paclitaxel (2–5, 6–8, 10–13). With regard to paclitaxel-induced

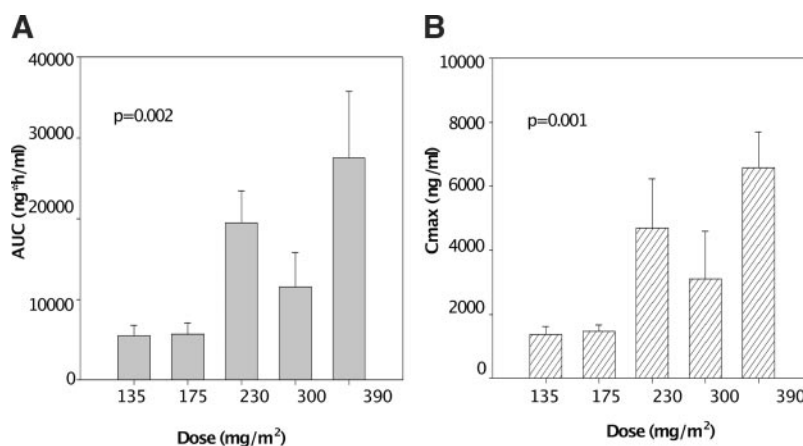
Table 6 Pharmacokinetic parameters of Genexol-PM^a

| Dose mg/m ² | 135 (n = 3) | 175 (n = 3) | 230 (n = 2) | 300 (n = 3) | 390 (n = 2) |
|--|---------------|---------------|----------------|----------------|----------------|
| C _{max} ^{ab} (ng/ml) | 1,357 ± 245 | 1,470 ± 208 | 4,682 ± 1,543 | 3,107 ± 1,476 | 6,567 ± 1,120 |
| AUC(0 → ∞) (ng·h/ml) | 5,473 ± 1,296 | 5,740 ± 1,391 | 19,476 ± 4,004 | 11,580 ± 4,277 | 27,490 ± 8,297 |
| t _{1/2} β (h) | 12.7 ± 4.2 | 12.5 ± 2.3 | 11.0 ± 1.9 | 11.4 ± 2.4 | 17.9 ± 1.0 |
| CL _T (L/h/m ²) | 25.5 ± 5.3 | 32.0 ± 8.8 | 12.1 ± 2.5 | 29.3 ± 13.8 | 14.9 ± 4.5 |

^a Data represent the mean ± SE.

^b C_{max}, peak plasma concentration; AUC, area under the plasma concentration-time curve; t_{1/2}β, elimination half-life; CL_T, total body clearance.

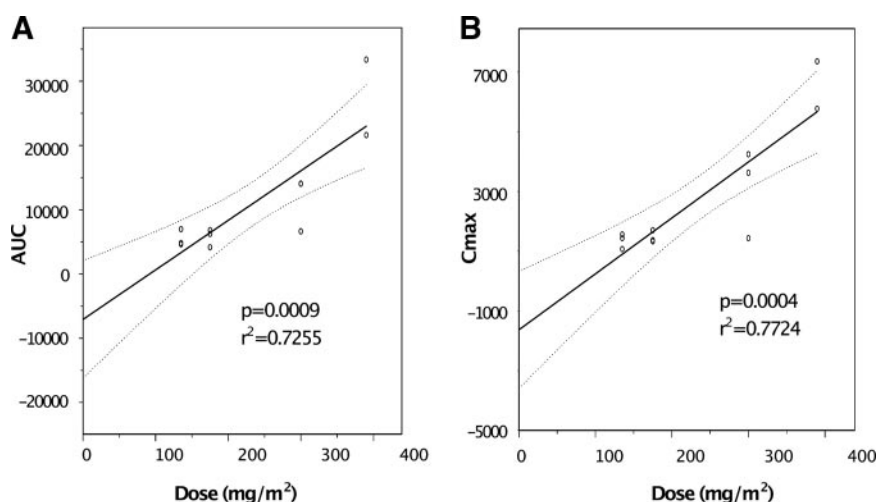
Fig. 3 The Genexol-PM area under the curve (AUC; A) and maximum paclitaxel concentration (C_{max}; B) versus dosage in each dose level; bars, ±SD.



HSR, CrEL is probably responsible, because other drugs formulated with it produce similar reactions, and CrEL-free paclitaxel does not cause HSR. Likewise, a growing body of evidence shows that CrEL itself is closely related with peripheral neuropathy, one of the main side effects reported for paclitaxel chemotherapy (28–30). The CrEL concentrations achieved by therapeutic doses of paclitaxel have been shown to produce axonal swelling, vesicular degeneration, and demyelination *in vivo* (31). Similarly, peripheral neuropathy is more augmented in short infusion because CrEL clearance increases by extending the infusion duration from 3 to 24 h (32). Besides these issues, CrEL-formulated vehicle is associated with pharmacokinetic paclitaxel alterations. CrEL has been shown to cause nonlinear pharmacokinetic paclitaxel behavior, because it inhibits the partition of paclitaxel from the vascular compartment to the tissues (6–8). As a result, the AUC and the plasma $T_{1/2}$ of CrEL-free paclitaxel tend to be relatively lower than that of conventional paclitaxel (32, 33). Accordingly, based on these observations of CrEL-related issues, it is strongly recommended that alternative formulation strategies should be pursued to allow a better control of toxicity and to enhance the pharmacological properties of paclitaxel.

Over the past few years, significant progress has been made in the development of alternative formulation of paclitaxel. The approaches used thus far include cosolvents, cyclodextrins, liposomes, and various conjugates such as polymer, docosahexanoic acid, polyglutamate, and albumin. Among these, the development of cosolvents or cyclodextrin-based formulations of paclitaxel has been hampered by paclitaxel precipitation and/or vehicle-related toxicities (14, 19). Similarly, a clinical development of PNU166945, a polymer-conjugated prodrug of paclitaxel, was prematurely discontinued due to its severe neurotoxicity (21). On the contrary, liposomes and some conjugate systems have shown encouraging preclinical and clinical results to replace the CrEL-based vehicle for paclitaxel delivery. Liposomal paclitaxel (34–36), docosahexanoic acid-paclitaxel (37, 38) and polyglutamate-paclitaxel conjugates (CT-2103; Refs. 39, 40) have common features of favorable toxicity profiles and targeted drug delivery to tumor sites. ABI-007, a human albumin-conjugated paclitaxel, was also well tolerated and showed some tumor responses in patients who had prior paclitaxel therapy (20). Compared with conventional paclitaxel, ABI-007 has been reported to be more effective in

Fig. 4 Scatterplots of area under the curve (AUC; A) and maximum paclitaxel concentration (C_{max}; B) versus each dose level of Genexol-PM, except at 230 mg/m². The — and ··· represent regression and 95% confidential values, respectively.



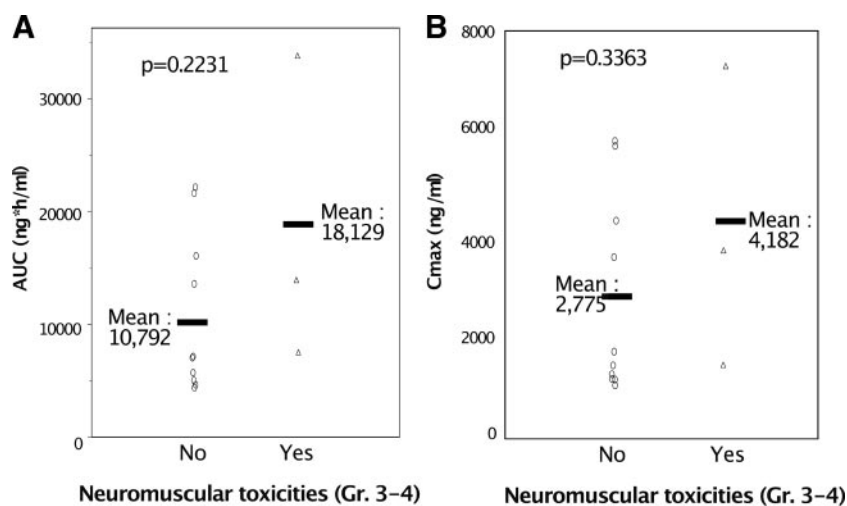


Fig. 5 Scatterplots depicting the relationship between the neuromuscular toxicities (grade 3–4) and area under the curve (AUC; A) and maximum paclitaxel concentration (C_{max}; B) of Genexol-PM. Toxicities were observed at level 3 (230 mg/m²) or higher.

terms of antitumor activity in metastatic breast cancer (41). In addition to aforementioned formulations, the polymeric micelles delivery system has also been considered to be an attractive formulation because of its nanoscopic size and preferential tumor distribution (22–25). Compared with the current paclitaxel, preclinical studies demonstrated that the polymeric micelle-formulated paclitaxel displayed a 3-fold increase in the MTD and a significantly increased antitumor efficacy (26). In the present phase I study, a novel taxane formulation without CrEL, Genexol-PM, was found to be nontoxic at dosages up to 300 mg/m². However, at the MTD of 390 mg/m², a variety of DLTs were observed, which included neuropathy, myalgia, and neutropenia. Because Genexol-PM is not formulated with CrEL, it is anticipated that both prophylaxis for HSR and in-line filtration would not be required. In the present study, the drug was safely administered in the outpatient setting over 3 h without prophylactic medication and without in-line filtration, as was expected. There was no HSR in any patient, although 1 patient at the dose level 2 experienced facial flushing shortly after starting infusion. Therefore, Genexol-PM appears to offer practical advantages in terms of safety and convenience due to no premedication and the avoidance of a specialized infusion device.

Regarding toxicities, the main side-effects of Genexol-PM were neutropenia and neuromuscular toxicity, in common with paclitaxel (1, 2). However, a lower incidence of myelosuppression was observed than that anticipated for an equivalent dose of paclitaxel. Grades 3–4 neutropenia were observed between dose levels 3 and 5 (230 and 390 mg/m²), but these were of short duration and normalized before the next cycle. In the case of Taxol, neutropenia is more common for 24-h infusion than for 3-h infusion, because CrEL clearance is increased according to time, and thus CrEL decreases the plasma paclitaxel concentration for the 3-h infusion, showing that paclitaxel-induced neutropenia is dependent on the presence of CrEL as well as the paclitaxel dosage (1, 2). Thus, the lower myelosuppressive effect of Genexol-PM can be explained in part by the absence of

CrEL. On the other hand, the neuromuscular toxicity of Genexol-PM seemed to be similar to CrEL-formulated paclitaxel. In particular, significant neurotoxicities were observed between 230 and 390 mg/m², and higher AUC and C_{max} in those groups showed a tendency to be associated with the development of severe neurotoxicity, indicating that Genexol-PM-induced neuropathy is more likely to be caused by the paclitaxel itself (13, 30). Similar to our findings, less myelosuppression and similar neuromuscular toxicity were observed in CrEL-free ABI-007 (20). However, a case of superficial keratopathy, which is a unique toxicity of ABI-007, was not observed for Genexol-PM.

In general, CrEL-free taxane formulations permit the administration of higher paclitaxel doses than conventional paclitaxel (20, 21, 42). The MTD of Genexol-PM was determined to be 390 mg/m² in the present study, and that of ABI-007 is 300 mg/m² (20). The achievement of a higher dose in the case of CrEL-free paclitaxel may be explained by the absence of the CrEL-mediated modulation of the pharmacokinetics of paclitaxel. The pharmacokinetics of Genexol-PM displays a tendency to be linear, except at a dose of 230 mg/m². It has been suggested that polymeric micelle nanoparticle drug carriers preferentially target tumor tissues, resulting in prolonged tumor exposure (24, 25, 43). As compared with conventional paclitaxel, Genexol-PM shows lower AUC and a shorter plasma half-life, suggesting the enhanced partitioning of Genexol-PM into the tissues and possibly more into the tumor beds. This observation is supported by the finding that the highest paclitaxel concentration was found in the tumor in a preclinical study of Genexol-PM (26). Accordingly, CrEL-free paclitaxel is expected to have significant advantages over conventional paclitaxel in terms of permitting the delivery of much higher doses and of having an enhanced tumor distribution. In the present study, the response rate of Genexol-PM was 14% (3 of 21), and disease stabilization was observed in 42% of patients refractory to conventional chemotherapy. Of 3 responders, 1 patient received regular dose of Genexol-PM (175 mg/m²), whereas

the remaining 2 received higher doses (230 and 300 mg/m²). Note that 2 patients treated at 175 or 230 mg/m² were taxane-failure. Therefore, it is conceivable that Genexol-PM is able to overcome taxane resistance either by the delivery of higher doses of paclitaxel or by an enhanced targeting to tumor tissues.

In conclusion, a novel taxane formulation, Genexol-PM, which is a CrEL-free paclitaxel formulated with a polymeric micelle, was safely administered without HSRs and showed a favorable toxicity profile. The major DLTs were neuromuscular toxicity and myelosuppression, and the recommended phase II dosage for Genexol-PM was determined to be 300 mg/m² for 3 h once every 3 weeks. Genexol-PM displayed the pharmacokinetics characteristic of CrEL-free paclitaxel. Of note, Genexol-PM permits the delivery of a higher paclitaxel dose. The achievement of higher paclitaxel dose without additional toxicity may suggest that this CrEL-free novel taxane formulation is likely to replace the current paclitaxel formulation. Phase II studies with Genexol-PM are currently underway for patients with advanced breast and non-small cell lung cancers.

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