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Nonlinear pharmacokinetics of paclitaxel in ovarian cancer patients

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KEY WORDS paclitaxel; pharmacokinetics; ovarian neoplasms

ABSTRACT

AIM: To characterize the disposition of paclitaxel in patients with ovarian carcinoma after a 3-h infusion. **METHODS**: Fifteen patients with advanced ovarian cancer were enrolled and were administered paclitaxel in a 3-h infusion at dosing levels of 135 mg/m^2, 175 mg/m^2, and 235 mg/m^2. Thirteen plasma samples were obtained during the infusion and up to 24 h after the infusion. Paclitaxel concentrations in plasma were determined by HPLC assay. Pharmacokinetic parameters were assessed with noncompartment model and model-dependent method. **RESULTS**: The disposition of paclitaxel in patients with ovarian cancer conformed to a two-compartment model. The main pharmacokinetic parameters of three groups were $T_{\frac{1}{2}\beta}$ (5.18 ± 3.49), (6.26 ± 2.21), and (6.99 ± 1.45) h, AUC (14.71 ± 0.76), (39.09 ± 13.10), and (66.52 ± 12.23) mg·h·L^{-1}, *Cl* (14.29 ± 0.74), (7.52 ± 2.15), and (6.25 ± 1.93) L·h^{-1}, respectively. **CONCLUSION**: The disposition of paclitaxel was nonlinear after a 3-h infusion. There was individual variability of metabolism among patients.

INTRODUCTION

Paclitaxel is extracted from the bark and needles of the Paclitafic Yew, *Taxus brevifolia*. All efforts for its synthetic and semisynthetic production have still not been successful. Paclitaxel, with its unique mechanism of action as an inducer of tubulin polymerization, has demonstrated impressive clinical antitumor activity in patients with breast, lung, head and neck, and advanced platinum-refractory ovarian carcinoma[1]. It appears to be one of the most promising agents for the first or second-line chemotherapy of gynecology solid tumors.

Paclitaxel has been studied extensively both experimentally and clinically. However, its complete pharmacokinetic profile in humans has not yet been fully understood. There is more to be known about its pharmacological disposition, metabolism, pharmacodynamics, and pharmacological interactions with other drugs, especially with other antineoplastic agents. The primary objective of this study was to characterize the disposition of paclitaxel in the patients with platinum-pretreated ovarian carcinoma.

MATERIALS AND METHODS

Patients Fifteen patients, mean age is 49.9 (34 - 60) a, mean weight is 57.6 (35.5 - 80) kg, and mean height is 159.6 (153 - 167) cm, histologically proven to have ovarian cancer. All patients had received at least one prior chemotherapy regimen containing cisplatin and/or carboplatin. No prior chemotherapy was given in the 4 wk before enrollment (or 6 wk for mitomycin, high-dose carboplatin). Other eligibility criteria showed as following: nonpregnant, nonlactating; with adequate hematopoetic counts (ANC > 2000 /μL; Platelet count > 100 000/μL); hepatic and renal function within the range of normal values; An Eastern Cooperative Oncology Group (ECOG) performance status ≤2.

Treatment and dosage escalation Ampoules that contained 30 mg paclitaxel formulated in Cremophor EL: ethanol (1:1, v/v) were provided by Bristol-Myers Squibb Co. Paclitaxel was diluted with 0.9 % sodium chloride or 5 % dextrose solution before administration. All solutions were administered through 0.22 μm cellulose acetate filters inline (IVEX II: Millipore, Molsheim, France). Patients were pretreated with 40 mg of dexamethasone, orally, 6 and 12 h before infusion, diphenhydramine 2 mg iv and ranitidine 50 mg iv 30 min before paclitaxel infusion.

Patients were administered at levels of 135 mg/m^2, 175 mg/m^2, or 235 mg/m^2 respectively, by a 3-h infusion. Blood samples were collected from the arm oppo-

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site to the one receiving the infusion. Thirteen plasma samples were obtained during the infusion and up to 24 h after the infusion. This was performed before the start of infusion, 1 h and 2 h after the start, and at 0, 10, 20, 30, 60 min, as well as 2, 4, 8, 12, and 24 h after the completion of the infusion.

Plasma sample assay The concentrations of paclitaxel in plasma were determined by HPLC assay. The HPLC system consisted of a model 510 pump (Waters Associates, Milford, MA) and Shim-pack CLC-ODS analytic column (4.6 mm × 150 mm; particle size 5 μm). Detection was performed with SHIMADZU UV-detector operating at 227 nm. A stock solution of paclitaxel with a concentration of 50 mg/L was prepared and stored at −70 ℃. Standard samples were prepared by making appropriate dilutions of the stock solution with blank plasma. Standard curves for paclitaxel were spanned over the concentrations from 0.03 to 5.00 μg/L. The calibration curve was calculated with the weighed (1/x) linear regression analysis. A 300μL aliquot of standard or unknown samples was mixed with diazepam (internal standard, IS), and then was extracted by tert-butyl methyl ether in a two-step extraction. The organic layer was evaporated under nitrogen stream at room temperature. The residual was reconstituted with mobile phase. Twenty μL reconstituted solution was injected into HPLC system and eluted with the mobile phase consisting of methanol: acetonitrile: water (25:40:39, v/v) at a rate of 1.2 mL·min^{-1}, and column elution was monitored at 227 nm. Concentrations of paclitaxel were calculated by estimating the ratio of paclitaxel signal to the internal standard signal in that sample and comparing the ratio with a concomitantly performed standard curve. The retention time for IS and paclitaxel was 9.6 and 12.2 min, respectively.

Pharmacokinetic analysis The pharmacokinetics of paclitaxel were evaluated by both noncompartmental model and model-dependent method with PCNONLIN 4.2 (SCI, 1992). This nonlinear, least-squares, iterative regression program determined slopes and intercept of the logarithmically plotted curves of multiexponential functions and provided a correlation coefficient of the fitted curve. Pharmacokinetic parameters explored included the plasma peak concentration (C_{max}), AUC, MRT, and V_{ss}.

RESULTS

The study developed a sensitive and specific HPLC assay for the determination of the concentration of paclitaxel in plasma. The chromatograph is shown in Fig 1. A linearity was obtained with concentrations ranging from 0.03 to 5.00 mg/L of paclitaxel with a good correlation coefficient ($r = 0.9999$, $n = 7$). The variations of within-run and between-run coefficients of variation were < 4.90 %, and the mean recoveries were 98.24 %, 103.34 %, and 97.42 % for the checked samples with three different concentrations, respectively.

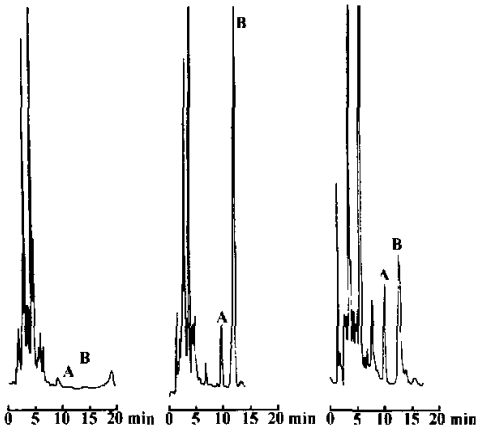

Fig 1. HPLC chromatogram of paclitaxel plasma: 1) blank plasma sample, 2) paclitaxel spiked plasma sample, 3) a plasma sample from a patient. Peak A is internal standard (T_R = 9.7 min). Peak B is paclitaxel (T_R = 12.2 min).

Pharmacokinetics of paclitaxel A total of 15 ovarian cancer patients were enrolled into the pharmacokinetic study of the trial. The median age of the patients was 50 (range, 34 to 60) with a median ECOG performance status of 1 (range, 0 to 2). The number of patients treated at each dosage level were as following: 135 mg/m^2, 3; 175 mg/m^2, 9; 235 mg/m^2, 3, respectively.

After IV administration, paclitaxel was rapidly eliminated from the central plasma compartment and was extensively distributed into the peripheral compartment despite of its relatively high plasma protein binding level (~95 %)[2]. Its plasma distribution curve (Fig 2) appeared to be biphasic, with mean $T_{\frac{1}{2}\beta}$ of (5.18 ± 3.49) h, (6.26 ± 2.21) h, and (6.99 ± 1.45) h for 135 mg/m^2, 175 mg/m^2, and 235 mg/m^2, respectively. Mean pharmacokinetic parameters for paclitaxel, as calculated by two-compartment methods, are listed in Tab 1. It was

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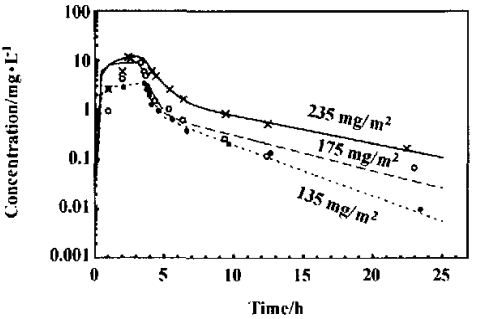

Fig 2. Representative patient concentration-versus-time profiles of paclitaxel during 3-h infusions.

Tab 1. Mean pharmacokinetic parameters for paclitaxel, as calculated by two-compartment model.

	135 mg/m² $n=3$	175 mg/m² $n=10$	235 mg/m² $n=3$
AUC/mg·h·L^{-1}	14.71 ± 0.76	39.09 ± 13.10	66.52 ± 12.23
C_{max}/mg·L^{-1}	3.10 ± 0.36	8.80 ± 3.51	16.34 ± 3.75
Cl/L·h^{-1}	14.29 ± 0.74	7.52 ± 2.15	6.25 ± 1.93
$T_{\frac{1}{2}\beta}$/h	5.18 ± 3.49	6.26 ± 2.21	6.99 ± 1.45
MRT/h	3.85 ± 2.57	3.07 ± 1.29	3.39 ± 0.67
V_{ss}/L	55.98 ± 39.91	23.45 ± 12.16	20.63 ± 4.71
$T_{\frac{1}{2}\alpha}$/h	0.18 ± 0.07	0.27 ± 0.09	0.71 ± 0.10
K_{12}	2.62 ± 1.59	0.79 ± 0.32	0.22 ± 0.08
K_{21}	0.32 ± 0.16	0.19 ± 0.10	0.15 ± 0.04

found that there was a great interpatient variation with the limited patient numbers. For dose in the 1∶1.30 proportion (135 mg/m²∶175 mg/m²), the mean AUC value increased in the ratio of 1∶1.66. The mean Cl was 14.29 ± 0.74 L/h for the 135 mg/m² dose, 7.52 ± 2.15 L/h for the 175 mg/m² dose, and 6.25 ± 1.93 L/h for the 235 mg/m² dose. This appears to be a nonlinear disposition.

The values of Vss in the study were much larger than the volume of total body water, indicating that paclitaxel binds extensively to plasma protein and/or other tissue elements, most likely tubulin. It was reported that paclitaxel could show an extensive binding to plasma protein, as determined by either equilibrium dialysis or ultrafiltration [protein binding ranging from (95 – 97) % over a wide range of drug concentrations], although the drug was still readily eliminated from the central compartment or plasma[2].

Our data suggests that paclitaxel clearance decreases with increasing dosage. Paclitaxel systemic elimination tends towards saturation and therefore AUC increases disproportionately with increasing dosage.

DISCUSSION

The data generated in the present study complements and expands previous knowledge of the clinical pharmacology of paclitaxel and has important practical implications for optimal clinical use. The nonlinear disposition of paclitaxel may have considerable impact on the clinical use of the drug. Increasing or decreasing the dose, with no concurrent adjustment of infusion time, will result in nonproportionally higher or lower C_{max} value and AUC. Longer or shorter infusion schedules may also result in nonproportionally lower or higher plasma concentration and AUC than that predicted for the same delivered dose of paclitaxel. The demonstration of nonlinearity suggests that new dose and schedules of paclitaxel should be based on suitable pharmacokinetic studies, which would help in the interpretation of possible unexpected clinical effects.

Systemic elimination of paclitaxel is saturated, and therefore AUC will increase disproportionately with increasing dosage at higher plasma concentrations. This indicates a limited capacity for enzymatic conversions of the parent drug as saturable kinetics. Liver metabolism may play an important role in the disposition of the drug. Recently, it was shown that 6α-hydroxylation is the prevalent biotransformation of paclitaxel in isolated human liver microsomes, where it is catalyzed by cytochrome P450-3A or -2C[3, 4]. As a consequence, the induction or inhibition of paclitaxel by other drugs metabolized by cytochrome P450-3A or -2C will eventually require dose adjustment to avoid under- or over- dosage. Paclitaxel thus can accumulate in the plasma of patients with hepatic impairment.

Saturable tissue distribution of paclitaxel has been postulated previously[5, 6]. The unusual pharmacokinetic characteristics imply that paclitaxel distributes freely into tissues in a linear (first order) fashion at low plasma concentration; However, once plasma concentration exceeds the K_m for distribution, less paclitaxel is able to enter peripheral tissues and more is available for elimination. Saturable cellular membrane transport processes, or saturable tissue binding process may be used to explain this phenomena.

In our study, the disposition of paclitaxel was clearly nonlinear and complex. When analyzing the paclitaxel concentration-versus-time data from patients, the mea-

sured C_{max} and the calculated AUC for three dose groups were higher than those reported with the same dose and schedule by investigators in USA and Europe[7]. The difference appears to be more clear at a relatively higher dose of 225 mg/m^2. This implies a tendency of race difference in paclitaxel metabolism and suggests that a lower dose would be needed for Chinese and Asian.

Furthermore, an optional therapeutic index should be considered to associate a range of plasma paclitaxel concentrations, *in light of demonstrated interpatient variability*. Paclitaxel plasma concentration should be lower than a threshold of 0.1 μmol/L at 24 h post administration for limiting its adverse effect. The pharmacodynamic model described by Michaelis-Menten kinetics can provide the basis for adaptive control with feedback dosing strategies to achieve optimum concentration in individual patients[8].

In summary, the metabolism of paclitaxel is variable among the patients. It seems there is a tendency of racial difference of metabolism between Chinese and Westerners[7]. To further optimize the clinical use of paclitaxel, larger groups of patients are needed to investigate in population pharmacodynamic and pharmacokinetic study. Our pharmacokinetic study is effective in predicting paclitaxel disposition, regardless of dose and schedule. It should facilitate further pharmacodynamic investigations. This study offers useful information for rational use of paclitaxel in Chinese.

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紫杉醇在卵巢癌化疗病人中的非线性药物动力学

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关键词 紫杉醇; 药代动力学; 卵巢肿瘤

目的: 探讨紫杉醇在卵巢癌病人体内的药物动力学特点. **方法**: 15名紫杉醇化疗病人3小时内输注剂量分别为135 mg/m^2, 175 mg/m^{2}和235 mg/m^2. 输注过程中及输注后24小时采集病人血样. 由非房室和房室模型评价药物动力学参数. **结果**: 化疗病人符合二室模型, 三组的 $T_{\frac{1}{2}\beta}$分别为(5.18 ± 3.49, 6.26 ± 2.21 和 6.99 ± 1.45) h, AUC (14.71 ± 0.76, 39.09 ± 13.10 和 66.52 ± 12.23) mg · h · L^{-1}, *Cl* (14.29 ± 0.74, 7.52 ± 2.15 和 6.25 ± 1.93) L · h^{-1}. **结论**: 紫杉醇具有非线性药物动力学特征, 病人的代谢存在个体差异.

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