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ORIGINAL ARTICLE

Phase I clinical and pharmacokinetic study of UTD1, a genetically engineered epothilone analog in patients with advanced solid tumors

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Abstract
Purpose The epothilones are a novel class of microtubule-stabilizing agents. UTD1 is an epothilone analog generated by genetic manipulation of the polyketide biosynthetic gene cluster. This phase I study was designed to evaluate the safety and pharmacokinetic(PK) profiles of UTD1 in patients with advanced solid tumors.
Patients and methods This was an open-label, single-arm, one site, phase I, dose-escalation study. Patients were treated with escalating doses of UTD1 as a 3-h intravenous infusion every 3 weeks.
Results Twenty-one patients were enrolled and received UTD1 at six dose levels ranging from 25 to 225 mg/m^2. Dose-limiting toxicity (DLT) was ataxia, and other frequent non-haematological toxicities were peripheral neuropathy, gastrointestinal disorders, fatigue, and myalgia/arthralgia. Myelosuppression was rare, with no grade 3 and 4 neutropenia, in contrast to paclitaxel and ixabepilone. The maximum-tolerated dose was established as 170 mg/m^2. Preliminary results showed linear pharmacokinetics along the range of doses tested. Prolonged disease stabilization was observed in patients with breast cancer, non-small lung cancer, and other cancers.
Conclusions The recommended phase II dose of UTD1 is 170 mg/m^2 as a 3-h infusion every 3 weeks. Ataxia was the DLT. UTD1 showed advantages over paclitaxel and Ixapebilone in relation to safety profile, especially myelosuppression. The acceptable tolerability warrants further phase II study.

Keywords Epothilone · MTD · DLT · Pharmacokinetics · UTD1

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Introduction

Microtubule is a well-recognized target for anticancer chemotherapy. The prototypical microtubule-stabilizing agent paclitaxel promotes tubulin polymerization, inhibits normal microtubule dynamics, and induces mitotic arrest and eventually apoptosis [1]. It has a demonstrated efficacy in the treatment of several types of solid tumors, including ovarian, breast, and lung cancers. However, its therapeutic application is partially limited by its safety profile and easy development of drug resistance. The development of taxane resistance is of particular concern when managing patients with metastatic breast cancer (MBC) since taxanes have been widely used in the adjuvant and neoadjuvant settings. It has resulted in the earlier emergence of taxane resistance and diminished response to these potent agents,

particularly in patients with MBC. Efforts to overcome taxane resistance have led to the search for new, more effective antimicrotubule therapies in the setting of MBC [2, 3].

The epothilones were originally isolated from the soil myxobacterium *Sorangium cellulosum* and belong to polyketide-derived 16-membered ring macrolides. They represent a new class of microtubule-stabilizing agents that may overcome drug resistance, including tumors resistant to paclitaxel. They share a similar mechanism of action with the taxanes, but are not substrates of the drug efflux proteins p-glycoprotein and the multidrug-resistance-associated protein-1 (MRP1) [3–5]. During the last decade, epothilones have become a hot spot for the development of antitumor drugs. Several epothilone derivatives are currently in different stages of clinical trials, and the first epothilone anticancer drug had been approved by FDA in 2007 [6].

UTD1 is an epothilone derivative generated by genetic manipulation of the epothilone biosynthetic gene cluster. It can be produced at high levels through fermentation of the engineered strains. Its structure is different from other epothilone analogs already appoved by FDA or currently in clinical trials. Based on the structure–activity relationship studies, the structure change in the molecule may offer a better safety profile and retain similar acitvity. UTD1 has demonstrated high activity in vitro and in vivo against a broad range of tumors, including paclitaxel-sensitive tumors (MCF-7, PC-3, NCI-H460, etc.) as well as multidrug-resistant human colon (HCT-15, LS1034), leukemia (CEM/C2, HL60/MX2), and breast (NCI/ADR-Res) carcinoma models(unpublished data). These data suggest that UTD1 may overcome multidrug resistance and offer improved clinical efficacy in both taxane-insensitive and taxane-sensitive cancers.

The primary objectives of this phase I study were to determine the maximum-tolerated dose (MTD), dose-limiting toxicity (DLT), toxicity profile, and the recommended phase II dose of UTD1 administered as a 3-h infusion every 3 weeks to patients with advanced solid tumors unresponsive to currently available therapies or with no known effective therapy. The pharmacokinetic (PK) evaluation of UTD1 was also performed.

Patients and methods

Eligibility

Patients $\geq$18 and $\leq$65 years old with histologically confirmed advanced solid tumors who had experienced treatment failure with one or more chemotherapy regimens or for whom standard systemic therapy did not exist were enrolled onto the study. Prior taxane therapy was allowed. Patients had at least one measurable or non-measurable but assessable lesion of disease as defined by the Response Evaluation Criteria in Solid Tumors. Eligible patients were required to have a Eastern Cooperative Oncology Group (ECOG) performance status score of $\leq$2 and life expectancy of at least 3 months. Eligible patients were also required to have normal renal function and adequate hepatic function (bilirubin $\leq 1.5 \times$ the upper limit of normal [ULN] and ALT or AST$\leq 5 \times$ ULN). Patients with impaired hematologic function, including platelet count less than 100×10^9/l and absolute neutrophil count less than 2.0×10^9/l, were not eligible. Patients were excluded from study entry if they had received chemotherapy within 4 weeks, had documented hypersensitivity reaction (HSR) to *Cremophor-EL*, or had history of brain metastases. The study was approved by the Institutional Review Board of Cancer Hospital, Chinese Academy of Medical Sciences, and all patients provided a signed informed consent for study participation as per institutional guidelines.

Study design

This was a open-label, single-arm, dose-escalation study to assess the safety and pharmacokinetics of UTD1 administered to patients with advanced solid tumors as a 3-h intravenous (i.v.) infusion every 3 weeks. The starting dose was 25 mg/m^2 determined on the basis of preclinical toxicology study. Dose escalation was based on toxicities from the first cycle for each cohort of patients. At least three patients were initially enrolled for each cohort except for the starting dose level. If none of the three patients experienced dose-limiting toxicity (DLT), the dose was escalated to the next level. If one of the initial three patients developed DLT, at least one additional patient was enrolled at the same dose. If one-third or more patients developed DLT at a given dose level, the dose was decreased to the previous dose level. The provisional MTD was defined as the dose level immediately below that at which one-third or more patients experienced DLT.

The following adverse events during cycle 1 were defined as DLTs: grade 4 neutropenia (ANC $<0.5 \times 10^9$/l) for >5 days; febrile neutropenia (fever of >38.5°C with ANC $<1.0 \times 10^9$/l); grade 4 thrombocytopenia (platelet count $<25 \times 10^9$/l); grade 3(platelet count $\geq 25 \times 10^9$/l and$<50 \times 10^9$/l)symptomatic thrombocytopenia requiring platelet transfusions; any other grade 3 non-hematologic toxicity related to UTD1.

Treatment and assessment

UTD1 was prepared for administration by dilution of the concentrated stock solution in 0.9% normal saline to a final

concentration of 0.5 mg/ml. The diluted drug was administered intravenously over 3 h every 21 days with hypersensitivity prophylaxis (diphenhydramine 50 mg and cimetidine 300 mg intravenous injection 30 min before UTD1 administration). Antiemetic premedication was not mandatory in the protocol.

Patients' assessment included physical examination, evaluation of ECOG, and tolerability to treatment. Complete blood counts and ECG were repeated weekly; blood chemistry was repeated every 3 weeks. Toxicity was graded according to the NCI Common Toxicity Criteria (CTC version 3.0). No more than six cycles of treatment were given after the first cycle if toxicities (except alopecia) had resolved to baseline or ≤grade 1 according to common toxicity criteria until either unacceptable toxicity or disease progression. Patients experiencing a DLT could continue UTD1 therapy, but the dose would be decreased to the previous dose level. Tumor response, evaluated according to the RECIST criteria, was assessed every two cycles or earlier in case of clinical progressive disease (PD); objective responses were confirmed 4 weeks apart.

Sample collection and pharmacokinetic analysis

Blood samples were obtained at −3 h (before the start of drug infusion), −2.5 and −2 h (during the infusion), and 0, 0.83, 0.25, 0.5, 1, 2, 4, 10, 24, 48, 72, and 96 h (after the end of infusion) during the first cycle. Samples were kept on ice, and plasma was separated by centrifugation at 4°C within 1 h of collection; plasma samples were stored at −80°C until analysis. Blank urine samples were collected predose; the other urine samples were collected from the start of drug infusion to 72-h postinfusion during the first cycle and kept at –20°C until analysis.

Plasma levels of UTD1 and a major metabolite of UTD1 (seco-UTD1) were measured by liquid chromatography (LC)/MS/MS using a validated assay with a lower limit of detection of 0.2 ng/ml. Pharmacokinetic parameters were calculated using non-compartmental methods, including peak concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration–time curve (AUC_{0-t}), area under the first moment curve ($AUMC_{0-t}$), mean residence time (MRT), terminal elimination half-life ($T_{1/2}$), total body clearance (CL), and apparent volume of distribution (Vd). AUC_{0-t} and $AUMC_{0-t}$ were determined by summing the areas from time zero to the time of last measured concentration, calculated using a log-trapezoidal method, and the extrapolated area. Elimination rate constant (k_e) was determined by the terminal log-linear phase of the plasma concentration–time curve. The elimination rate constant (k_e) was also used to estimate the apparent terminal elimination half-time, $T_{1/2} = \ln 2/k_e$. CL was determined by dividing dose by AUC_{0-t}. Vd was calculated by dividing CL by k_e. MRT was determined as the area under the first moment curve divided by AUC_{0-t}.

Results

Patient characteristics

Between October 2007 and August 2008, a total of 21 patients were enrolled onto the trial. All 21 patients received at least one cycle of UTD1 and were eligible for toxicity assessment. Demographic and disease characteristics of these patients are listed in Table 1. The most common primary tumor types were breast ($n = 10$) and non-small cell lung ($n = 4$) cancers. Nearly all (91%) of the patients had received prior chemotherapy, with 81% receiving two or more prior chemotherapy regimens. Of the 19 patients who received prior chemotherapy, 13 patients (68%) had received taxanes. Eleven patients (52%) had

Table 1 Patient characteristics

Characteristics	No. of patients ($n = 21$)
Gender	
Male	5
Female	16
Age (years)	
Median	48
Range	25–64
ECOG performance status	
0	10
1	11
Tumor type	
Breast cancer	10
NSCLC	4
Malignant melanoma	2
Cystosarcoma phyllodes	1
Colorectal cancer	1
PNET	1
Carcinoma of submaxilary gland	1
Small cell malignant tumor in left scapular area	1
Previous treatment	
Chemotherapy	19
No. of prior regimens	
1	2
≥2	17
Prior taxane therapy	13
Prior radiotherapy	11
Surgery only	1

ECOG Eastern co-operative oncology group, *NSCLC* non-small cell lung cancer

Table 2 Dose-escalation scheme and number of cycles given of UTD1

Dose level (mg/m^2)	No. of patients	No. of cycles
25.0	2	5
50.0	3	10
85.0	3	10
125.0	6	19
170.0	3	5
225.0	4	4
#225.0 decreased to 170.0	#4	8
Total	21	61

Patients who experienced DLT continued on UTD1 therapy, and the dose was decreased to the previous dose level

received prior radiotherapy. Eighteen patients (86%) remained on study for at least two cycles. Doses were held or decreased during these two cycles.

Toxicities and DLT

Six dose levels of UTD1, starting from 25 mg/m^2, then escalated to 50, 85, 125, 170, and 225 mg/m^2, were evaluated in this study. Table 2 shows patient distribution and number of cycles received by dose levels. A total of 61 cycles were administered to 21 patients, with a median of three cycles per patient (range, 1–6). Eighteen patients (86%) received at least two cycles, and four patients (19%) received six cycles. At the 125 mg/m^2 dose level, one of the three patients experienced grade 3 nausea and/or vomiting. Therefore, three additional patients were treated at this dose level, and none of them experienced DLT. The only other significant toxicity among the six patients treated at this dose level was grade 2 peripheral sensory neuropathy during the second cycle in two patients with prior taxane therapy. At the 225 mg/m^2 dose level, one of three patients in first cohort experienced DLT (grade 3 ataxia, lasting for 70 h) and another one experienced grade 3 nausea and/or vomiting. An additional patient who was recruited and treated at this dose level also experienced grade 3 ataxia. Consequently, enrollment was stopped, and grade 3 ataxia was therefore identified as the DLT of this study. The provisional MTD and the recommended dose for phase II evaluation were determined to be 170 mg/m^2 as a 3-h i.v. infusion every 3 weeks.

The incidence of toxicities by dose level is shown in Table 3. There was minimal hematologic toxicity observed in this heavily pretreated patient population. One colorectal cancer patient in the 125 mg/m^2 cohort experienced grade 2 neutropenia. There were no other hematologic toxicities attributed to the study drug. Therefore, it seems that UTD1, when administered using a 3-h i.v. infusion, 3-weekly administration schedule, is not associated with clinically significant myelosuppression.

Of two breast cancer patients in the 225 mg/m^2 cohort who experienced DLT(grade 3 ataxia), one of them received two cycles of paclitaxel as first-line treatment that had completed over 6 months before study entry and presented grade 3 ataxia in the first cycle of UTD1. Ataxia started 40 h after treatment and lasted for 70 h. The second patient received six cycles of paclitaxel in combination with adjuvant that had ended over 1 year before study entry and developed ataxia 48 h after treatment of UTD1. Symptoms progressively worsened up to grade 3 in the subsequent 6 h and lasted for 60 h. Ataxia was not observed in these patients at the subsequent cycles after dose reduction to 170 mg/m^2.

The most common non-hematologic adverse events were fatigue, neurotoxicity, gastrointestinal discomfort, and myalgia/arthralgia, all reported in more than 50% of patients in the first cycle. Peripheral neurotoxicity with UTD1 was characterized by paresthesia in a symmetric, glove-and-stocking distribution. Paresthesia was dose

Table 3 Drug-related toxicities (in any cycle)

Dose level (mg/m^2)	No. of patients														
	Neutropenia		Hyperbilirubinemia		Fatigue		Paresthesia/ neurotoxicity		Myalgia/ arthralgia		Gastrointestinal discomfort		Ataxia[a]		Alopecia
	G1–2	G3–4	G1–2	G3–4	G1–2	G3–4	G1–2	G3–4	G1–2	G3–4	G1–2	G34	G1–2	G3–4	G1–2
25.0	–	–	–	–	–	–	–	–	–	–	1	–	–	–	–
50.0	–	–	–	–	–	–	–	–	–	–	1	–	–	–	–
85.0	–	–	–	–	2	–	3	–	2	–	2	–		–	–
125.0	1	–	1	–	3	–	5	–	5	–	4	1	–	–	2
170.0	–	–	–	–	3	–	3	–	3	–	3	–	–	–	2
225.0	–	–	–	–	4	–	4	–	4	–	3	1	–	2	4
Total (% of patients)	1 (4.7)		1 (4.7)		12 (57)		15 (71)		14 (67)		16 (76)		2 (9.5)		8 (38)

[a] DLT, G represents grade

dependent and cumulative:at 85–125 mg/m^2, its incidence during the first cycle was 89% and severity never exceeded grade 1; grade 2 paresthesia was experienced by 57% of patients treated at 170–225 mg/m^2. Overall, paresthesia recovered after about 3–12 months since last dosing of UTD1. Fifteen patients (71%) experienced arthralgia, myalgia, or both. The first occurrence of arthralgia/myalgia was reported at 85 mg/m^2, manifested by muscular limb pain starting 48 h after treatment and lasting for 48–72 h. Pain was usually manageable using non-steroidal anti-inflammatory drugs (NSAIDs). The most frequently reported gastrointestinal discomfort included transient, manageable, mid-to-moderate anorexia, and nausea with or without vomiting. Fatigue typically occurred during the 1 week of each treatment cycle and usually resolved before the next treatment cycle. No patient experienced hypersensitivity reactions following UTD1 administration.

Antitumor activity

Among the 18 patients eligible for response evaluation, six patients achieved stable disease from 12 to 18 weeks, including the following three advanced breast cancer: one NSCLC, one carcinoma of submaxilary gland, and one small cell malignant tumor in left scapular area. There were no complete response or partial responses seen.

Pharmacokinetic studies

The pharmacokinetic profile of UTD1 in plasma was assessed in all patients treated at 25–225 mg/m^2 during the first cycle. The mean pharmacokinetic parameters of UTD1 or its major metabolite seco-UTD1 are summarized in Tables 4 and 5. The concentrations of UTD1 or seco-UTD1 in plasma in relation to time postinfusion are shown in Figs. 1, 2. As it is clear from Fig. 1 and Table 4, AUC_{0-t} values appeared to increase in proportion to the dose level, and $T_{1/2}$ was similar among the six dose level subgroups and did not change with dose. The mean CL values ranged from 200 to 383 ml/min/m^2; mean Vd values were in the range from 4.2 to 14.6l (Table 4). However, there were no statistically significant differences among six dose level subgroups ($P > 0.05$). These results showed linear pharmacokinetics along the range of doses tested with a elimination half-life of about 14 h, which is relatively short in comparison with that of Ixempra and Epo906 [3–5].

We can see from Fig. 2 and Table 5 that C_{max} (range 124.4–11,185.8 μg/l) and AUC_{0-t} (range 1,693–62,599 μg h/l) increased in a greater than dose-proportional manner. Although $T_{1/2}$ was not significantly different among the six dose level subgroups ($P > 0.05$), $T_{1/2}$ of seco-UTD1 at 225 mg/m^2 group was about twice as long as the $T_{1/2}$ at 25 mg/m^2 group. These results showed that

Table 4 Mean pharmacokinetic parameters of UTD1

Dose level (mg/m^2)	T_{max} (h) Mean ± SD	C_{max} (μg l^{-1}) Mean ± SD	$AUC_{(0-t)}$ (μg h l^{-1}) Mean ± SD	$AUMC_{(0-t)}$ (μg h^2 l^{-1}) Mean ± SD	$MRT_{(0-t)}$ (h) Mean ± SD	$t_{1/2}$ (h) Mean ± SD	CL (l/h) Mean ± SD	Vd (l) Mean ± SD
25.0	3 ± 0	639.0 ± 64.1	2,205 ± 64	22,259 ± 3,601	10.1 ± 1.3	9.8 ± 1.3	0.29 ± 0.01	4.2 ± 0.7
50.0	3.0 ± 0.1	1,743.7 ± 342.2	4,782 ± 1,536	41,936 ± 15,963	8.6 ± 0.8	11.3 ± 0.9	0.29 ± 0.10	4.7 ± 1.6
85.0	3.03 ± 0.1	1,963.5 ± 1,208.8	6,468 ± 2,898	49,378 ± 18,740	7.9 ± 0.9	16.1 ± 1.7	0.41 ± 0.22	9.8 ± 6.7
125.0	3.0 ± 0.1	737.2 ± 1,139.2	9,452 ± 2,899	77,025 ± 1,863	8.8 ± 0.6	15.0 ± 1.7	0.37 ± 0.12	8.1 ± 3.2
170.0	3.0 ± 0.0	2,617.6 ± 936.8	13,186 ± 7,988	100,076 ± 73,772	7.4 ± 1.3	16.2 ± 1.7	0.42 ± 0.24	10.2 ± 6.3
225.0	2.5 ± 1	2,612.8 ± 1,079.4	14,126 ± 5,920	106,406 ± 45,699	7.8 ± 1.5	14.6 ± 0.9	0.53 ± 0.4	14.6 ± 0.9

Table 5 Mean pharmacokinetic parameters of seco-UTD1

Dose level (mg/m^2)	T_{max} (h) Mean ± SD	C_{max} (μg l^{-1}) Mean ± SD	$AUC_{(0-t)}$ (μg h l^{-1}) Mean ± SD	$AUMC_{(0-t)}$ (μg h^2 l^{-1}) Mean ± SD	$MRT_{(0-t)}$ (h) Mean ± SD	$t_{1/2}$ (h) Mean ± SD	CL (l/h) Mean ± SD	Vd (l) Mean ± SD
25.0	3.4 ± 0.2	124.4 ± 12.2	1,693 ± 4	29,344 ± 965	17.4 ± 0.5	14.7 ± 1.1	0.38 ± 0.00	6.2 ± 1.6
50.0	3.8 ± 0.3	397.5 ± 91.7	4,233 ± 1,352	75,820 ± 34,396	17.4 ± 3.2	18.7 ± 2.4	0.33 ± 0.11	8.8 ± 3.2
85.0	3.4 ± 0.1	1,322.9 ± 1,129.9	8,223 ± 6,259	110,225 ± 85,800	13.0 ± 1.7	13.0 ± 1.7	0.42 ± 0.32	7.7 ± 4.9
125.0	3.2 ± 0.2	3,001.6 ± 949.7	16,928 ± 5,354	239,297 ± 96,160	14.1 ± 2.3	23.2 ± 13.3	0.21 ± 0.12	8.4 ± 9.8
170.0	3.1 ± 0.1	4,328.1 ± 466.7	20,353 ± 2,908	206,659 ± 32,224	10.2 ± 0.7	20.4 ± 0.4	0.22 ± 0.14	6.4 ± 0.9
225.0	3.1 ± 0.1	11,185.8 ± 4,497.8	62,599 ± 38,755	743,259 ± 57,8806	11.4 ± 2.1	27.8 ± 8.3	0.13 ± 0.14	5.3 ± 4.7

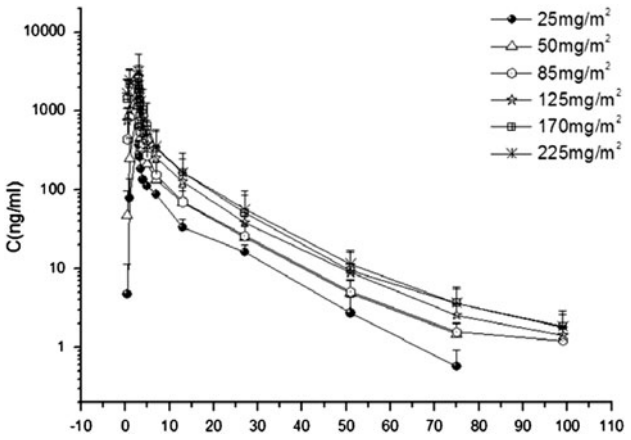

Fig. 1 The plasma concentration–time profiles of UTD1

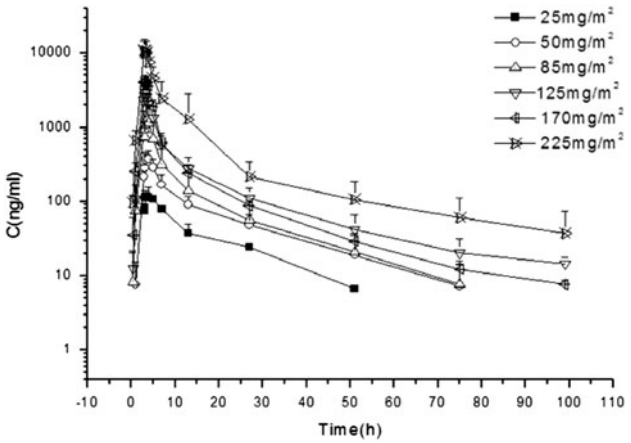

Fig. 2 The plasma concentration–time profiles of seco-UTD1

pharmacokinetics of seco-UTD1 were non-linear. In vitro cytotoxicity assays indicated that seco-UTD1 was not active toward different human cancer cell lines (unpublished data).

UTD1 was not detected in the collected urine samples of the treated patients, and the major metabolite seco-UTD1 detected in the urine accounted for only 1.1%, suggesting that UTD1 is metabolized and distributed extensively within the body.

Discussion

The attractive preclinical profile has made epothilones important lead compounds in the search for improved cytotoxic anticancer drugs. Recently, a wealth of new epothilone analogs has been developed. In addition to EPO906 (Patupilone, the natural epothilone B), there are at least five other compounds, which are currently at different stages of clinical evaluation [4, 7–13]. Of these, ixabepilone (BMS-247550;Ixempra) has been approved by the US FDA as monotherapy for the treatment of metastatic breast cancer resistant or refractory to anthracyclines, taxanes, and capecitabine, or in combination with capecitabine for patients with advanced breast cancer resistant to anthracyclines and taxanes using a same schedule as in this study [14].

This dose-escalation trial in patients with advanced solid tumors who had failed standard therapy, UTD1 was administered as a 3-h i.v. infusion every 21 days at doses ranging from 25–225 mg/m^2. Grade 3 ataxia was the DLT, and the MTD was established at 170 mg/m^2 on this dosing schedule. The results of this study demonstrate that UTD1 was safe and well tolerated. The toxicity profile associated with 3-weekly administration is strikingly different from that of the taxanes, and the first approved epothilone drug Ixempra: myelosuppression of any type was rare with UTD1 in this study, consistent with the observations in preclinical toxicological evaluation (unpublished data). The most common adverse events were fatigue and gastrointestinal in nature, which were generally mild and not dose limiting. Neurotoxicity and myalgia/arthralgia were also common adverse events in this study. They included both transient pains in the extremities and myalgias, as well as the more common sensory disturbances frequently observed with antimicrotubule agents. These toxicities were of grade 1 or 2 and were not dose limiting. Although paresthesia was more frequently reported in patients (9/15 patients) who had previously received taxanes, based on these limited observations, we could not conclude whether there was a correlation between previous taxane exposure and development of neuropathy. Paclitaxel and ixabepilone are associated with hypersensitivity reactions because of its Cremophor-EL formulation even with premedication treatment [13, 15]. Since UTD1 formulation also contains Cremophor-EL, there have been some concerns that hypersensitivity reactions could occur. We did not observe, however, any case of hypersensitivity reactions in our patients. The reasons for this lack of hypersensitivity may include the routine premedications and much less Cremophor-EL used in the formulation. Reports from other phase I and II studies of ixabepilone showed that the most common toxicities leading to dose reduction or discontinuation were myelosuppression, neuropathy, and fatigue [11–14]. Paclitaxel is associated with significant schedule-dependent neutropenia, especially in heavily pretreated patients [16]. Docetaxel is associated with dose-limiting myelosuppression, with the majority of patients experiencing grade 4 neutropenia [17]. Compared with these agents, UTD1 seems to have an improved safety profile and is not associated with any significant myelosuppression. Although no patient was removed from the current study due to toxicity alone, the evaluation of long-term toxicity for UTD1 was limited by the fact that more than one-half

of patients were removed from the study within two cycles of treatment due to progressive diseases.

The DLT of UTD1 administered as a 3 h i.v. infusion every 21 days is ataxia. In contrast to clinical data, no ataxia and other obvious neuropathic toxicities were observed in our preclinical toxicology studies. No ataxia occurred at the MTD and lower doses in this trial, even UTD1 was given more than 6 cycles; accordingly, ataxia is likely to be a very low-frequency adverse event at lower dose levels of UTD1, and treatment with UTD1 is safe at MTD and below dose.

The mechanism for this toxicity needs to be further study. Given the relatively short half-life of UTD1 and its metabolite when compared to Ixempra and Epo906, it may be related to the peak levels of UTD1 or dose above threshold. Another explanation for this may attribute to species difference or difficulty in identifying peripheral neurotoxicity in animals. It was generally believed that ataxia is a reflection of neurotoxicity. A trial with a modified schedule may further improve the clinical activity and explain the mechanism of ataxia of UTD1.

Another epothilone analogue under development, sagopilone (ZK-EPO) has just finished its phase I studies and got the results published recently [18, 19]. In these trials, weekly or 3-weekly administration of sagopilone over 30 min or 3 h has been investigated. Similar toxicity profile was observed including gastrointestinal reactions, myalgia/arthralgia, and neurotoxicity. For 3-weekly schedule with 3-h infusion, 5 of 9 patients experienced grade 3 peripheral sensory neuropathy and 2 out of 9 had grade 3 neutropenia under recommended phase II dose levels, which seems to be more problematic than our compound. Although no ataxia was reported in 3-h infusion arm, two patients in the 30-min arm suffered from central ataxia with one in grade 3. Again, together with our data, it indicates that although ataxia is relatively rare adverse event, it is an epothilone-related toxicity that should draw our attention.

This study showed that, after intravenous administration, time to reach C_{max} (T_{max}) of UTD1 was about 3 h which was very close to what had been reported in ixabepilone of 2.97 h but longer than sagopilone around 2 h. This can be partially explained by better water solubility of sagopilone, which allows formulation without Cremophor-EL [18, 20, 21]. The mean maximum serum concentration (C_{max}) and area under the plasma concentration–time curve (AUC_{0-t}) of UTD1 seem to increase in proportion to dose. The terminal elimination half-life ($T_{1/2}$) of UTD1, ranged from 9.8 to16.1 h, was similar among the six dose level subgroups and did not change with dose. These results showed linear pharmacokinetics of UTD1 along the range of doses tested. Systemic exposure to seco-UTD1, the major metabolic product, is not negligible, the C_{max} and AUC_{0-t} of seco-UTD1 seem to increase unproportionally to dose. It was noted that $T_{1/2}$ of UTD1 was relatively shorter than other epothilone derivatives; however, since this is a small sample size early phase study involving several types of cancer, results of these pharmacokinetic evaluations should be interpreted with caution and further studies of alternative dosing schedules are warranted.

Although neither complete response nor partial response was observed, prolonged disease stabilization for at least 12 weeks was observed in patients with breast cancer, non-small lung cancer, and others. To some extent, no objective response may be due to that most patients were heavily pretreated, especially more than one-half of them had received taxanes. The preclinical data and preliminary results of this study suggest that UTD1 has activity even in tumor types typically are refractory to taxanes. Given that UTD1 has a relatively short half-life when compared to Ixempra and Epo906, a trial with a modified schedule may further improve the clinical activity of UTD1.

In conclusion, UTD1 appears well tolerated at the recommended phase 2 dose with fatigue, gastrointestinal toxicity, and peripheral neurotoxicity being the most common adverse events. Myelosuppression was rare, with no grade 3 and 4 neutropenia. The DLT of UTD1 administered as a 3 h i.v. infusion every 21 days is ataxia. UTD1 showed linear pharmacokinetics along the range of doses tested. The MTD and the recommended phase II dose of this novel agent on this schedule are 170 mg/m^2. The acceptable tolerability of UTD1 demonstrated in this phase I study is encouraging. In addition, based on our preclinical studies, UTD1 not only showed excellent cytotoxic activity toward many human MDR cancer cell lines, but also demonstrated potent efficacy toward MDR cancer models in nude mice with inhibition of tumor growth as high as 89%(unpublished data). This ability for UTD1 to overcome drug resistance in non-clinical studies makes it of interest to test whether we can see the same in its future clinical trials.

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Conflict of interest None.

References

1. Horwitz SB (1992) Mechanism of action of taxol. Trends Pharmacol Sci 13(4):134–136
2. Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN (2007) Overview of resistance to systemic therapy in patients with breast cancer. Adv Exp Med Biol 608:1–22

3. Xu BH (2008) Epothilones in the treatment of breast cancer: review of clinical experience. Asia-Pac J Clin Oncol 4(Suppl. 3):S30–S39
4. Fumoleau P, Coudert B, Isambert N et al (2007) Novel tubulin-targeting agents: anticancer activity and pharmacologic profile of epothilones and related analogues. Ann Oncol 18(Suppl. 5):v9–v15
5. Goodin S, Kane MP, Rubin EH (2004) Epothilones: mechanism of action and biologic activity. J Clin Oncol 22(10):2015–2025
6. Thomas ES, Gomez HL, Li RK et al (2007) Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol 25(33):5210–5217
7. Lee JJ, Swain SM (2008) The epothilones: translating from the laboratory to the clinic. Clin Cancer Res 14(6):1618–1624
8. Altmann KH, Memmert K (2008) Epothilones as lead structures for new anticancer drugs–pharmacology, fermentation, and structure-activity-relationships. Prog Drug Res 66:275–334
9. Larkin JM, Kaye SB (2007) Potential clinical applications of epothilones: a review of phase II studies. Ann Oncol Suppl 5:v28–v34
10. Fornier MN (2007) Epothilones in breast cancer: review of clinical experience. Ann Oncol Suppl 5:v16–v21
11. Dawson NA (2007) Epothilones in prostate cancer: review of clinical experience. Ann Oncol Suppl 5:v22–v27
12. Puhalla S, Brufsky A (2008) Ixabepilone: a new chemotherapeutic option for refractory metastatic breast cancer. Biologics 2(3):505–515
13. Fornier MN (2007) Ixabepilone, first in a new class of antineoplastic agents: the natural epothilones and their analogues. Clin Breast Cancer 7(10):757–763
14. Ho J, Zhang L, Todorova L et al (2009) Budget impact analysis of ixabepilone used according to FDA approved labeling in treatment-resistant metastatic breast cancer. J Manag Care Pharm 15(6):467–475
15. Weiss RB, Donehower RC, Wiernik PH et al (1990) Hypersensitivity reactions from taxol. J Clin Oncol 8(7):1263–1268
16. Finley RS, Rowinsky EK (1994) Patient care issues: the management of paclitaxel-related toxicities. Ann Pharmacother 28(5 Suppl):S27–S30
17. Fossella FV, DeVore R, Kerr RN et al (2000) Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 non-small cell lung cancer study group. J Clin Oncol 18(12):2354–2362
18. Schmid P, Kiewe P, Possinger K et al (2010) Phase I study of the novel, fully synthetic epothilone sagopilone (ZK-EPO) in patients with solid tumors. Ann Oncol 21(3):633–639
19. Arnold D, Voigt W, Kiewe P et al (2009) BWeekly administration of sagopilone (ZK-EPO), a fully synthetic epothilone, in patients with refractory solid tumours: results of a phase I trial. Br J Cancer 101(8):1241–1247
20. Aghajanian C, Burris HA 3rd, Jones S et al (2007) Phase I study of the novel epothilone analog ixabepilone (BMS-247550) in patients with advanced solid tumors and lymphomas. J Clin Oncol 25(9):1082–1088
21. Shimizu T, Yamamoto N, Yamada Y et al (2008)) Phase I clinical and pharmacokinetic study of 3-weekly, 3-h infusion of ixabepilone (BMS-247550), an epothilone B analog, in Japanese patients with refractory solid tumors. Cancer Chemother Pharmacol 61(5):751–758