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CLINICAL TRIAL REPORT

A phase I trial of UCN-01 and prednisone in patients with refractory solid tumors and lymphomas

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Abstract
Purpose UCN-01 potently inhibits protein kinase C, phosphatidylinositide-dependent kinase-1, and checkpoint kinase 1, which are involved in regulating cell cycle progression. We designed a phase I study to determine the maximum tolerated dose (MTD) of UCN-01 with prednisone in patients with advanced malignancies.
Methods UCN-01 was administered as a continuous intravenous infusion over 72 h in cycle 1 and 36 h in subsequent cycles. Prednisone was given orally at 60 mg/m^2 per day for five consecutive days within each 28-day cycle. Standard dose escalation was employed, and MTD was defined as the dose at which no more than one of six patients experienced a dose-limiting toxicity (DLT). Plasma pharmacokinetics of UCN-01 were assessed.
Results Fifteen patients received a total of 55 courses of treatment. The MTD and the recommended phase II dose of UCN-01 in this combination is 72 mg/m^2 total dose over 72 h for cycle 1 followed by 36 mg/m^2 per cycle over 36 h. All patients experienced hyperglycemia but responded to insulin treatment. Hypophosphatemia was a DLT in two patients. There were no cumulative toxicities. No objective responses were observed, but five patients had stable disease, including two patients with lymphoid malignancies who had prolonged disease stabilizations. UCN-01 has a long terminal half-life and low clearance; there was wide inter-patient variability in peak concentrations.
Conclusion UCN-01 can be safely administered in combination with prednisone without unacceptable toxicity. The prolonged stable disease in two patients with lymphoid malignancies is a proof of principle for the evaluation of cyclin-dependent kinase inhibitors in oncology.

Keywords Cyclin-dependent kinase inhibitor · Protein kinase C · Phase I · Combination chemotherapy · UCN-01 · Prednisone

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Introduction

Cyclin-dependent kinases (cdks) are regulators of cell cycle progression, a pathway that is dysregulated in a number of cancers. Cdk alterations include hyperactivation due to overexpression of regulatory cyclins, decreases in endogenous cdk inhibitors (e.g., INK4 family proteins), or loss or inactivation of cdk substrate retinoblastoma family proteins [13, 21, 24]. Thus, inhibition of cdks is an attractive target for cancer therapeutics. There are several classes of direct cdk small molecule inhibitors, including

staurosporines, nonspecific protein kinase inhibitors derived from *Streptomyces staurosporeus*.

UCN-01 (7-hydroxystaurosporine; NSC 638850) is a selective inhibitor of protein kinase C (IC_{50} 4–30 nmol/L) and other kinases [19]. UCN-01 mediates multiple cellular effects that might explain its antiproliferative antitumor activity in preclinical models. Treatment with UCN-01 in vitro results in cell cycle arrest in G1 or S phase [22, 26]; induction of apoptosis by inhibition of phosphatidylinositol phosphate-dependent kinase-1 (PDK1) [18]; and sensitization of cancer cells to the DNA-damaging effects of certain chemotherapeutic agents [2, 4, 14, 23].

Based on these promising preclinical data, the safety of UCN-01, administered as a 72-h continuous infusion, was evaluated in a single-agent phase I clinical trial in patients with refractory neoplasms at the National Cancer Institute (NCI) [20]. One partial response (PR) was observed in a patient with melanoma, and prolonged disease stabilization (>2.5 years) was achieved in a patient with alk-positive anaplastic large-cell lymphoma. Additionally, a patient with chemotherapy-resistant B cell lymphoma who received one cycle of UCN-01 and was taken off study for disease progression, subsequently had a complete remission following rechallenge with EPOCH chemotherapy; it was felt that UCN-01 may have sensitized the lymphoma to the cytotoxic agents [28]. In that NCI trial, UCN-01 treatment was initially administered as 72-h infusions every 2 weeks because preclinical data demonstrated that at least 72 h of exposure were required to achieve growth inhibition in certain cell lines. However, in the first nine patients treated on this regimen, unexpectedly high drug exposures were observed with long elimination half-lives and extremely low systemic clearance, felt in part to be secondary to high-affinity binding of UCN-01 to a human plasma protein, alpha-1-acid glycoprotein (hAAG) [7, 8]. This led to a modification of the schedule to administer UCN-01 as a 72-h infusion for the first cycle followed by a 36-h infusion, thus reducing the administered dose by 50% for the second and subsequent cycles. This was the schedule that was ultimately evaluated and the maximum tolerated dose (MTD) established in the single-agent phase I trial, which formed the basis for designing the current combination trial. This single-agent regimen was well tolerated, and the principal grade 3 or greater toxicities were hyperglycemia, nausea, vomiting, and pulmonary dysfunction with hypoxia in the absence of infiltrates. UCN-01 has also been evaluated as a 3- or 72-h infusion in phase I trials in combination with topotecan, irinotecan, carboplatin, cisplatin, and fluorouracil in patients with advanced solid tumors and in a phase II trial with topotecan in patients with advanced, recurrent ovarian cancer [6, 9–12, 16, 27].

The purported clinical benefit in a patient with lymphoma in the single-agent trial at the NCI generated interest in combining UCN-01 with lymphoma-directed therapies, including regimens containing prednisone or a similar corticosteroid. However, since hyperglycemia was the principal toxicity observed in single-agent trials of UCN-01 [5, 20] and is a recognized side effect of prednisone therapy, it raised concerns about the tolerability of the combination. Also, prednisolone, the active metabolite of prednisone, is known to bind to hAAG and could potentially raise the unbound fraction of UCN-01 by competitively binding to the plasma protein. Thus, we designed this phase I trial of UCN-01 plus prednisone to assess the combination's safety and toxicity, establish the MTD, and evaluate the pharmacokinetics (PK) of UCN-01 when delivered in this combination.

Patients and methods

Eligibility criteria

Patients (age ≥ 18 years) were eligible for this study if they had pathologically confirmed metastatic or unresectable malignancy for which there were no acceptable standard therapies; an Eastern Cooperative Oncology Group performance status ≤2; adequate organ and bone marrow function defined as absolute neutrophil count ≥1,000/μL, platelets ≥100,000/μL, total bilirubin ≤1.5× the upper limit of normal (ULN), aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤2.5× ULN, and creatinine ≤1.5× ULN; and 12-h fasting glucose ≤110 mg/dL or between 110 and 140 mg/dL with hemoglobin A_1C ≤6.5 mg/dL.

Prior anticancer therapy must have been completed at least 4 weeks (6 weeks for nitrosoureas and mitomycin C) before starting the study drug; toxicities were required to have recovered to eligibility levels.

Patients were excluded if they had an uncontrolled intercurrent illness; were pregnant or lactating; had brain metastases within the past 6 months; or had a history of diabetes, hyperglycemia, or interstitial lung disease within the last year. Other exclusion criteria included a history of duodenal or gastric ulcer or severe gastritis within the past 6 months (due to the risk of exacerbation by prednisone), symptomatic congestive heart failure, or unstable angina pectoris.

The protocol design and conduct followed all applicable regulations, guidance, and local policies. All patients gave their informed consent prior to inclusion in the study.

Trial design

This was an open-label, single-arm phase I study of UCN-01 in patients with advanced malignancies. UCN-01 was

supplied by the Division of Cancer Treatment and Diagnosis, NCI under a Collaborative Research and Development Agreement with Kyowa Hakko Kogyo, Japan. UCN-01 was administered as an inpatient treatment by continuous IV infusion (CIV) for 72 h on days 3–5 of the first cycle with prednisone administered at a dose of 60 mg/m^2 daily orally for five consecutive days (days 1–5; total dose/cycle = 300 mg/m^2). Starting with cycle 2, UCN-01 was administered as an outpatient treatment via CIV over 36 h beginning on day 3 of the cycle; the prednisone dose and schedule remained the same throughout. Treatment cycles were repeated every 28 days (±7 days), and the dose escalation for UCN-01 occurred as shown in Table 1. The starting dose of UCN-01, 17 mg/m^2 per day, was 50% of the dose associated with grade 4 toxicity in the single-agent phase I trial. All toxicities observed at the 17 mg/m^2 per day dose level in that trial were mild and reversible, other than grade 3 hyperglycemia, which was also easily managed. Following the starting dose, doses were escalated in approximately 40% increments.

Adverse events were graded according to NCI Common Toxicity Criteria version 2.0. Dose-limiting toxicities (DLTs) were defined as grade 3 or 4 non-hematologic toxicities (excluding hyperglycemia, grade 3 metabolic acidosis in the presence of grade 3 or 4 hyperglycemia, and grade 3 or 4 metabolic abnormalities that returned to grade 1 or less in 24–48 h), grade 4 granulocytopenia, and grade 4 thrombocytopenia. DLT definitions for hyperglycemia and metabolic acidosis associated with hyperglycemia included the following: grade 3 hyperglycemia lasting >4 days, grade 4 hyperglycemia lasting >1 day, or metabolic acidosis with pH <7.25 (with grade 3 or 4 hyperglycemia) for >1 day. Hyperglycemia was graded as follows: grade 1 >ULN–160 mg/dL; grade 2 >160–250 mg/dL; grade 3 >250–500 mg/dL; grade 4 >500 mg/dL.

Three to six patients were entered at each dose level. If none of the three patients experienced a DLT, subsequent patients were enrolled at the next higher dose level. If one of three patients experienced a DLT, three additional patients were added at that dose level, for a total of six patients. If two of three or two of six patients experienced a DLT, no further patients were started at that dose level, and the dose level was determined to have exceeded the MTD. Three additional patients were then entered on the next lower dose level. The MTD was defined as the dose at which no more than one of six patients or ≤33% experience a DLT (one dose level below the dose at which at least two of three to six patients experience DLT).

Safety and efficacy evaluations

A complete medical history and physical examination were performed prior to study entry and at the beginning of each cycle. Complete blood counts with differential and serum chemistries were performed at baseline, several times during week 1 of first two cycles, and weekly during the rest of study. Plasma glucose levels were checked frequently: during cycle 1, each morning, before meals, and each night during the 3 days of infusion and then weekly thereafter; during cycle 2 and beyond, before breakfast on day 4, and then weekly thereafter. At the first documentation of serum glucose >200 mg/dL, an insulin drip was initiated and titrated to keep serum glucose <140 mg/dL. Radiographic evaluation was performed every two cycles to assess for tumor response based on the Response Evaluation Criteria in Solid Tumors (RECIST) [25].

Sample collection for PK analysis

Serial blood samples were collected using an indwelling heparin lock starting on the third day of cycle 1 before UCN-01 dosing; 12, 24, 48, and 72 h after the start of infusion; and 12, 24, and 48 h after the end of infusion. During cycle 2, samples were collected before prednisone dosing, before UCN-01 dosing, 36 h after the start of infusion, and 24 h after the end of infusion. Blood samples were collected in tubes containing heparin, centrifuged (1,200×g for 5 min at 4°C), and the plasma layer stored at −80°C until analysis. Plasma samples were analyzed to determine UCN-01 concentrations using a previously published, validated assay employing high-performance liquid chromatography (HPLC) assay with UV detection [3]. Serum samples were collected on day 3 for assessment

Table 1 Dose escalation for UCN-01

Dose level	Cycle 1 infusion[a]	Total dosage per cycle	Cycle 2 and beyond infusion[b]	Total dosage per cycle
1	17 mg/m^2/24 × 72 h	51 mg/m^2	17 mg/m^2 × 24 h, then 8.5 mg/m^2 × 12 h	25.5 mg/m^2
2	24 mg/m^2/24 × 72 h	72 mg/m^2	24 mg/m^2 × 24 h, then 12 mg/m^2 × 12 h	36 mg/m^2
3	34 mg/m^2/24 × 72 h	102 mg/m^2	34 mg/m^2 × 24 h, then 17 mg/m^2 × 12 h	51 mg/m^2

[a] Total duration = 72 h

[b] Total duration = 36 h

of hAAG performed by Quest Diagnostics Nichols Institute (San Juan Capistrano, CA, USA).

PK data analysis

Plasma UCN-01 concentration versus time profiles were evaluated by noncompartmental analysis (NCA) using WinNonlin Pro v. 5.0 (Pharsight, Mountain View, CA, USA). The peak concentration (C_{max}) and time to peak (t_{max}) were determined by visual inspection of the concentration–time profiles. The terminal rate constant (λ_z) was determined by linear regression of the terminal linear portion of the log concentration–time curve. λ_z was evaluated using at least three concentration time points of the terminal phase. The terminal half-life ($t_{1/2}$) was calculated by $0.693/\lambda_z$. The area under the concentration versus time curve (AUC_{0-t}) from time zero to the last measurable time concentration (C_t) was calculated by linear-trapezoidal interpolation. The area extrapolated to infinity ($AUC_{0-\alpha}$) was calculated from $AUC_{(0-t)} + C_t/\lambda_z$. Total clearance ($CL_{tot}$) and volume of distribution ($V_{\lambda z}$) were calculated as dose/$AUC_{c-\alpha}$ and dose/($AUC_{c-\alpha} \times \lambda_z$), respectively.

Results

Patient characteristics

A total of 15 patients were enrolled in the study (Table 2) from February 2003 to June 2005. Response assessments were available for all patients. None of the 15 patients had a response as defined by RECIST criteria. A total of five patients had stable disease for longer than two cycles. Two patients, one with small lymphocytic lymphoma (SLL) and one with thymoma, had prolonged disease stabilizations lasting 18 and 8 months, respectively. The patient with SLL had disease progression following multiple combination chemotherapy regimens.

Table 2 Patient characteristics and demographics

No. of patients	15
Age range (years)	30–64
Sex	
Female	2
Male	13
ECOG performance status	
0	2
1	11
2	2
No. of prior chemotherapies	
Range	1-6
Mean	3
Tumor types	
Lymphomas	4
Anaplastic large cell lymphoma	1
Peripheral T cell lymphoma	1
Small lymphocytic lymphoma	1
Hodgkin's lymphoma	1
Melanoma	2
Nasopharyngeal cancer	1
Thymoma	1
Metastatic adenocarcinoma	5
Colorectal adenocarcinoma	1
Squamous cell cancer of the head and neck	1

Table 3 Grade 2 or higher adverse events felt to be related to study drugs

Adverse event	Grade (no. of patients)
Hyperglycemia	2 (9)
	3 (6)
Hypophosphatemia	2 (6)
	3 (4)
Visual (photophobia)	2 (1)
Headache	2 (1)
Hyponatremia	3 (1)
Hypoalbuminemia	2 (2)
Rash/desquamation	2 (1)
Myelosuppression	
Leucopenia	2 (1)
	3 (1)
Neutropenia	2 (1)
Anemia	2 (1)

Toxicity

Patients received a total of 55 courses of treatment at three different dose levels. No cumulative toxicities were observed. All toxicities of grade 2 and higher that were felt to be drug related are listed in Table 3. Two of the six patients on dose level 3 (102 mg/m^2 total dose over 72 h for cycle 1 followed by 51 mg/m^2 per cycle) developed grade 3 hypophosphatemia during cycle 1; these events were felt to be related to the study drug and were considered DLTs. The dose was reduced to level 2 (72 mg/m^2 total dose over 72 h for cycle 1 followed by 36 mg/m^2 per cycle), and a total of six patients were treated at this dose level without any DLTs, establishing UCN-01 72 mg/m^2 total dose for cycle 1 followed by 36 mg/m^2 per cycle along with prednisone 60 mg/m^2 per day for 5 days every cycle as the MTD. There were no grade 4 adverse events. All patients developed some grade of hyperglycemia. Six

patients developed grade 3 hyperglycemia, of whom three were on dose level 3 (102 mg/m^2 total dose over 72 h for cycle 1 followed by 51 mg/m^2 per cycle) and two were on dose level 2 (72 mg/m^2 total dose over 72 h for cycle 1 followed by 36 mg/m^2 per cycle). All patients who developed grade 3 hyperglycemia were treated with insulin and had resolution of hyperglycemia.

Pharmacokinetic analysis

UCN-01 plasma PK data were obtained from all 15 patients during cycle 1 and from 9 patients during cycle 2. The first-dose PK parameters are summarized by dose level in Table 4. At the dose range investigated (17, 24, and 34 mg/m^2 per 24 × 72 h), wide inter-patient variability was noted. UCN-01 exhibited an increase in peak concentration (C_{max}) as the dose increased; the concentration–time profiles of UCN-01 were characterized by C_{max} occurring at end of infusion followed by a slow decline in plasma concentration, hence a very long estimated terminal half-life (286–547 h; Table 4) (the half-life of UCN-01 may be underestimated in this study due to the repeat dosing after 28 days). Overall, the clearance was extremely low (2.13–5.47 mL/h per m^2). Day 3 serum hAAG concentrations were available for six patients and ranged from 96 to 158 mg/dL. An inverse correlation was observed between serum hAAG concentrations and UCN-01 clearance ($P = 0.049$), as has been reported previously.

Discussion

The MTD and the recommended phase II dose of the combination of UCN-01 with prednisone is UCN-01 72 mg/m^2 total dose CIV over 72 h for cycle 1 followed by 36 mg/m^2 per cycle CIV over 36 h along with prednisone 60 mg/m^2 per day for 5 days every cycle. As a single agent on the same schedule the MTD for UCN-01 was 127.5 mg/m^2 over 72 h followed by 63 mg/m^2 total dose administered over 36 h. The next higher dose level of 159 mg/m^2 over 72 h was associated with grade 4 hyperglycemia and vomiting, thus exceeding the MTD. Combining UCN-01 with prednisone in our trial resulted in a reduction in the maximum dose of UCN-01 that could be safely administered by 44%. Given the single-agent data, it was not surprising that we observed some degree of hyperglycemia in the majority of patients. Clinically, hyperglycemia was well managed with insulin, and we did not observe an associated metabolic syndrome. Staurosporine has been shown to inhibit insulin-stimulated glucose transport and reduce transport of the human insulin-responsive glucose transporter to the plasma membrane [15, 17]. In the single-agent clinical trial of UCN-01 conducted at the NCI, the underlying mechanism of UCN-01-induced hyperglycemia was studied and was considered to be due to peripheral tissue resistance to insulin and not a reduction in insulin secretion, as immunoreactive C peptide levels increased with the onset of hyperglycemia [20]. Unlike the single-agent trial of UCN-01, we did not observe any pulmonary toxicity. In spite of the addition of prednisone, we also did not observe any significant GI toxicity. The DLT of hypophosphatemia has also been observed in a phase I trial of UCN-01 in combination with irinotecan [10].

The pharmacokinetics of UCN-01 in combination with prednisone are consistent with previously published data for the single-agent UCN-01, suggesting that co-administration of prednisone does not appreciably change the PK of UCN-01. We observed a mean C_{max} of approximately 12 μg/mL with prolonged half-life of approximately 450 h at the MTD. C_{max} increased with increasing doses; however, the increase in exposure was less than dose-proportional, consistent with previous findings [7]. This has been attributed to the saturable protein binding of UCN-01 to hAAG. The plasma concentration achieved is within the range of IC_{50} values of UCN-01 against several tumor types in preclinical models [1, 22]. The prolonged half-life of UCN-01 in humans has been explained based on the high-affinity binding of UCN-01 to hAAG [7]. Inter-patient variability in C_{max} correlated with plasma concentrations of hAAG in a separate clinical trial [11]. This raises a concern about the amount of free or unbound UCN-01 in plasma, which, like for many drugs, may be a more important determinant of drug activity than total drug concentrations. This was addressed in the single-agent UCN-01 trial at the NCI in which the plasma was ultracentrifuged and the

Table 4 Pharmacokinetic parameters after 72-h IV infusion with UCN-01

Dose (mg/m^2/24 h)	C_{max} (μg/mL)				AUC_{inf} (h × μg/mL)				Clearance (mL/h/m^2)				$t_{1/2}$ (h)			
	Mean	Range	SD	*n*	Mean	Range	SD	*n*	Mean	Range	SD	*n*	Mean	Range	SD	*n*
17	10.0	6.3–13.2	3.5	3	3126	3109–3143	23.5	2	5.4	5.4–5.5	0.04	2	314	302–325	16.4	2
24	11.8	8.0–15.6	2.6	6	8432	5462–11268	2692	4	3.1	2.1–4.4	1.0	4	450	371–547	83.0	4
34	17.2	13.4–19.4	2.2	6	8349	6670–9330	1461	3	4.2	3.6–5.1	0.8	3	379	286–533	134	3

amount of UCN-01 in supernatant assessed as a measure of "free" drug [20]. At the doses of UCN-01 equivalent to the MTD in our trial (24 mg/m^2 per day for 3 days), "free" UCN-01 levels of 200–600 nmol/L were detected at the end of infusion. These levels are higher than the concentrations that were evaluated in preclinical studies that demonstrated synergism between UCN-01 and certain chemotherapeutic agents [14].

The multiple mechanisms of action of UCN-01, including cell cycle arrest and induction of apoptosis, as well as potential synergism with certain chemotherapeutic agents, make a case for the potential further evaluation of UCN-01 in combination regimens for cancer therapeutics. The prolonged disease stabilizations observed in two patients with a lymphoid malignancy (SLL and thymoma) support the evaluation of cdk inhibitors for patients with lymphoproliferative malignancies; several other cdk inhibitors are currently being evaluated [13].

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Conflict of interest statement None.

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