Modulation of Cell Cycle Progression in Human Tumors: A Pharmacokinetic and Tumor Molecular Pharmacodynamic Study of Cisplatin Plus the Chk1 Inhibitor UCN-01 (NSC 638850)

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Abstract

Background: UCN-01, a Chk1 inhibitor, abrogates S and G2 arrest and enhances cancer cell killing by DNA-damaging drugs in preclinical models. UCN-01 avidly binds α1-acid glycoprotein in plasma; whether sufficient drug concentrations are achieved in human tumors is unknown. A phase I trial tested the hypothesis that UCN-01 abrogates cisplatin-induced cell cycle arrest (in tumors) at tolerable doses.

Methods: Patients with advanced cancer received i.v. cisplatin, followed 22 hours later by UCN-01 (3-day continuous i.v. infusion of a 28-day cycle). Platinum was measured by atomic absorption, UCN-01 by high-performance liquid chromatography, and cell cycle progression in tumor biopsies by geminin immunostaining (biomarker for S/G2 phases of cell cycle).

Results: The first two patients treated with cisplatin (20 mg/m2 plus UCN-01 45 mg/m2/d) experienced dose-limiting toxicities (subarachnoid hemorrhage, hyperglycemia, hypoxia, cardiac ischemia, and atrial fibrillation). Following 25% UCN-01 dose reduction, no toxicities greater than grade 2 were seen. Median plasma UCN-01 half-life (T1/2) was 405 hours. Salivary UCN-01 concentrations showed a rapid initial decline (median T1/2a, 29.9 hours), followed by a terminal decay parallel to that in plasma. UCN-01 pharmacokinetics, and the timing of clinical toxicities, suggest that UCN-01 is bioavailable despite α1-acid glycoprotein binding. Marked suppression of cells in S/G2 in tumor biopsies was seen by geminin immunohistochemistry, suggesting that UCN-01 is bioavailable at concentrations sufficient to inhibit Chk1.

Conclusions: Cisplatin (30 mg/m2), followed 22 hours later by UCN-01 (34 mg/m2/d for 3 days), is well tolerated clinically and yields UCN-01 concentrations sufficient to affect cell cycle progression in tumors.
long plasma terminal half-life of UCN-01 was observed, and this was attributed to extensive binding to α1-acid glycoprotein (AAG) in human plasma (15, 18, 19). UCN-01 showed much greater binding to human AAG compared with other species (mice, rats, and dogs; refs. 18, 20). Consequently, the UCN-01 administration schedule was revised to a 28-day cycle, with the infusion reduced to 36 hours (i.e., 50% of the dose) for the second and subsequent cycles. Pulmonary toxicity, lactic acidosis with hyperglycemia, nausea/vomiting, and transaminitis were dose limiting (15). Concentrations of UCN-01 in human plasma greatly exceeded those required for cell cycle checkpoint abrogation, but whether UCN-01 was bioavailable to tissue or bound to plasma protein (especially AAG) could not be reliably determined.

Based on these observations, we initiated a phase I clinical trial to test the hypothesis that cisplatin-induced cell cycle arrest in human tumors could be abrogated by UCN-01 at clinically tolerated doses. A phase I accelerated dose titration trial was planned, with cisplatin given at escalating doses in combination with UCN-01 at its single-agent minimum tolerated dose (MTD; 45 mg/m²/d) by a 72-hour continuous i.v. infusion. After unexpectedly severe toxicities were seen in the initial dose cohort, the UCN-01 dose was reduced and subsequent patients received 34 mg/m²/d for 3 days. Enrollment of patients on the 3-day inpatient continuous infusion protocol was later discontinued administratively, in deference to a new study of cisplatin combined with UCN-01 given as a 3-hour outpatient infusion. Despite early closure of the original study, pharmacokinetic and pharmacodynamic data obtained from patients on the 3-day schedule provided important, novel insights regarding translation of cisplatin plus UCN-01 into the clinic, and modulation of cell cycle progression in patients.

**Patients and Methods**

**Eligibility.** The study protocol was approved by the Dartmouth College Committee for the Protection of Human Subjects, and by the Cancer Therapy Evaluation Program, National Cancer Institute (NCI; Bethesda, MD). Eligible patients were adults with histologically proven advanced solid tumors, not considered potentially curable with standard therapies; Karnofsky performance status ≥60; at least one tumor site accessible for serial biopsy prior to and during study treatment; estimated creatinine clearance ≥60 mL/min (by either Cockcroft formula, or by creatinine clearance as measured using a 24-hour urine collection); normal bilirubin, transaminases <2.5× upper limit of normal; WBC ≥4,000/mm³, absolute neutrophil count ≥2,000/mm³, and platelet count ≥150,000/mm³. Major exclusion criteria included more than two prior chemotherapy regimens; prior cumulative cisplatin dose ≥250 mg/m²; current peripheral neuropathy (any cause) >grade 1; any history of coronary artery disease or class III or IV congestive heart failure (New York Heart Association Classification); clinically significant hearing loss; or brain metastases. Pregnant or lactating women were ineligible, and all subjects were required to use contraception appropriately. Informed consent was obtained and documented for all subjects prior to entry into the study, in accordance with local institutional and federal human subjects regulations.

**Study treatment regimen.** Patients were admitted to the Hematology-Oncology Special Care Unit at Dartmouth-Hitchcock Medical Center for treatment. Cisplatin was administered over 1 hour by i.v. infusion following prophylactic antiemetics (dolasetron, 100 mg i.v.) and hydration with 0.9% normal saline (plus supplemental potassium and magnesium); hydration was continued for 2 hours post-cisplatin. Twenty-two hours after completion of the cisplatin infusion, UCN-01 was initiated and administered by 3-day continuous i.v. infusion via a central venous catheter. Treatment cycles were repeated every 28 days. Due to its extensive AAG binding and prolonged plasma half-life, UCN-01 was given at half the dose (i.e., over 36 hours rather than 72 hours) on cycle two and subsequent cycles. A modified accelerated dose titration design, as proposed by Simon and colleagues, was planned (21); conventional phase I dose increments and cohort sizes were triggered by the occurrence of dose-limiting toxicity in any patient. Toxicity was graded according to the NCI common toxicity criteria, version 2.0.

**Pharmacokinetic sampling.** All pharmacokinetic blood samples were obtained from a peripheral venous site and all chemotherapy given via the central venous catheter. For cisplatin, blood samples (10 mL) were taken at 0, 1, 1.5, 2, 4, and 6 hours following initiation of the cisplatin infusion. Blood samples were ultrafiltered by centrifugation using a 30,000 molecular weight cutoff Amicon Microcon centrifugal filter device (model YM-30; Millipore Corp., Bedford, MA) and stored at −70°C until analysis. For UCN-01, 10 mL of blood and 3 to 5 mL of saliva (stimulated using a standard procedure with 2% aqueous citric acid) were obtained at 0, 24, 48, 72, 168 (1 week), 336 (2 weeks), 504 (3 weeks), and 682 hours (i.e., time zero in the second treatment cycle) following initiation of the UCN-01 infusion. After preliminary results were obtained, additional salivary samples for UCN-01 were obtained at 96, 120, and 144 hours. The same pharmacokinetic sampling regimen was employed for patients who received a second treatment cycle. Blood and saliva samples for UCN-01 were processed in glass tubes (UCN-01 binds to plastic) and then stored at −70°C until analysis.

**Measurement of platinum in plasma ultrafiltrate.** Free platinum concentrations in the plasma ultrafiltrate was measured using a Perkin-Elmer 2380 atomic absorption spectrophotometer (Perkin-Elmer, Norwalk, CT), in the Irradiation Shared Resource of the Norris Cotton Cancer Center at Dartmouth. This assay had a lower limit of detection of 0.02 μg/mL of platinum. The inter-day coefficient of variation for this assay was 3.1% to 14.3%, over the range of the standard curve (0.05-10 μg/mL).

**Measurement of UCN-01 concentrations in plasma and saliva.** Measurement of UCN-01 in plasma and saliva was done by a modified high-performance liquid chromatography assay, based on the method described by Bauer and coworkers (22). UV absorbance detection was set at 295 nm for UCN-01 and 323 nm for umbelliferone (an internal standard). The coefficient of determination (r²) for the UCN-01 plasma concentration calibration curves exceeded 0.995 in all cases. The lower limit of detection was 0.5 μg/mL with a lower limit of quantification of 1 μg/mL. The intra-day assay coefficient of variation for UCN-01 was <5% and the inter-day assay coefficient of variation ranged from 5% to 13% and the inter-day assay coefficient of variation ranged from 2.4% to 11.2%. Saliva samples were processed and analyzed in a similar manner, except that fluorescence detection was used in place of UV absorbance. The detector excitation wavelength was set at 290 nm and the emission wavelength was 400 nm. The coefficient of determination (r²) for the UCN-01 saliva concentration calibration curves exceeded 0.996 in all cases. The lower limit of detection of this assay was 0.25 ng/mL with a lower limit of quantification of 0.5 ng/mL. The intra-day assay coefficient of variation ranged from 2.1% to 11.6% and the inter-day assay coefficient of variation ranged from 3.4% to 14.2%.

**Pharmacokinetic data analysis.** The pharmacokinetic data analysis for cisplatin and UCN-01 was done initially by inspection of semilogarithmic plots of free platinum and UCN-01 (in plasma and saliva) concentration-time data. Data were analyzed using a non-compartmental model (model 202) and standard pharmacokinetic variables estimated using WinNonlinPro 4.1 software (Mountain View, CA) running on a Pentium-based PC. For salivary UCN-01, Cmax, and Tmax were obtained from the raw concentration-time data. The apparent terminal decay rate was estimated using log-linear regression of the last three to four salivary samples. The initial decay rate was estimated by classical curve stripping and log-linear regression of the subsequent
Dose titration and toxicity. The first two patients treated (cisplatin 20 mg/m² combined with UCN-01 45 mg/m²/d) experienced serious adverse events that were considered dose-limiting toxicities. Patient no. 1 experienced grade 3 subarachnoid hemorrhage in the fourth week following investigational therapy. CT, MRI, and angiography showed no potentially predisposing anatomic abnormalities. Patient no. 2 experienced multiple adverse events including grade 3 cardiac ischemia, atrial fibrillation, hypoxia, and grade 4 hyperglycemia (a known UCN-01 toxicity). This patient experienced sudden-onset atypical chest pain, 2 to 3 hours in duration and not relieved by nitrates, ~6 hours after the end of the UCN-01 infusion. EKG showed atrial fibrillation and suggested inferolateral ischemia. Serial cardiac creatine phosphokinase and troponin levels remained within the reference range. The patient spontaneously converted to normal sinus rhythm 48 hours after discontinuation of study drugs, he had a normal cardiac stress test ~6 months prior to entering this study.

Several of these toxicities were previously associated with UCN-01 administration (15, 17, 23, 24) and were not typical for cisplatin; hence, the UCN-01 dose was reduced by 25%. Subsequently, five patients tolerated either cisplatin 20 mg/m² (n = 3) or cisplatin 30 mg/m² (n = 2) combined with UCN-01 34 mg/m²/d for 3 days without dose-limiting toxicities. Non–dose-limiting toxicities were mild (predominantly grade 1) and expected, based on the reported single-agent toxicities of the two drugs. Three patients (patient nos. 3, 6, and 7) received two cycles of treatment; no patient received more than two cycles of treatment.

Pharmacokinetics of UCN-01 in plasma and saliva. The plasma and salivary concentrations of UCN-01 over time during the first cycle of treatment are shown in Fig. 1. The pharmacokinetic variables for plasma and salivary UCN-01 derived from these data are summarized in Table 1. Summary data for our patients were consistent with values obtained for patients treated at the UCN-01 single-agent MTD, in the NCI phase 1 trial (15, 19). The median UCN-01 Cmax occurring at or after the end of the infusion in all patients, was 30.7 μmol/L (range, 19.9–58.5). UCN-01 avidly binds to human AAG, and this contributes to its extremely slow elimination (15, 18–20). The median AAG concentration was 970 mg/L (~20 μmol/L assuming a molecular weight of 50,000), and there was a strong correlation between plasma Cmax and plasma AAG (r² = 0.76; P = 0.004). Interestingly, the first two patients who experienced dose-limiting toxicities had lower UCN-01 Cmax values (19.9 and 25.4 μmol/L) than reported in the NCI trial (median, 36.4; range, 26.3–49.5), consistent with the relatively low AAG concentrations.

Table 1. Summary pharmacokinetics of UCN-01 in plasma and saliva

<table>
<thead>
<tr>
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<th>Median (n = 7)</th>
<th>Range (n = 7)</th>
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<tr>
<td><strong>Plasma pharmacokinetics</strong></td>
<td></td>
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<tr>
<td>Cmax (μmol/L)</td>
<td>30.7</td>
<td>19.9-58.5</td>
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<tr>
<td>T1/2 (h)</td>
<td>405.2</td>
<td>260.4-731.4</td>
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<tr>
<td>AUC (μmol/L h)</td>
<td>11,316</td>
<td>9,718-54,073</td>
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<tr>
<td>Clr (L/h)</td>
<td>0.046</td>
<td>0.007-0.055</td>
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<tr>
<td>Vdz (L)</td>
<td>19.0</td>
<td>7.76-27.02</td>
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<tr>
<td>AAG (mg/L)</td>
<td>970 (~20 μmol/L)</td>
<td>832-2,887</td>
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<tr>
<td><strong>Saliva pharmacokinetics</strong></td>
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<tr>
<td>Tmax (h)</td>
<td>72</td>
<td>49-96</td>
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<tr>
<td>Cmax (μmol/L)</td>
<td>0.041</td>
<td>0.013-0.214</td>
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<td>T1/2α (h)</td>
<td>29.9</td>
<td>16.2-80.7</td>
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<td>T1/2β (h)</td>
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<td>185.3-693.6</td>
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<tr>
<td>AAG (mg/L)</td>
<td>15 (~300 nmol/L)</td>
<td>10-20</td>
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![Image](image-url)
levels in our patients (19.7 and 17.4 μmol/L) versus those in the NCI phase I trial (median, 1,320 mg/L; range, 630-2,770; refs. 15, 19).

Salivary concentrations of UCN-01 over time for all patients are also shown in Fig. 1. A feature common to all these profiles was a prompt increase in $C_{\text{max}}$ (median, 41 nmol/L; range, 13-214) at or just after the end of the UCN-01 infusion. This was followed by a biphasic decay with an initial rapid decline (median half-life of 29.9 hours; range, 16.2-80.7 hours) and a slower decline paralleling the plasma UCN-01 profile (median half-life of 254 hours; range, 185-694 hours). The median UCN-01 concentration in saliva during this terminal phase was $0.05\%$ of that in plasma at this point. There was no significant relationship between the plasma AAG and either salivary UCN-01 $C_{\text{max}}$ ($r^2 = 0.15; P = 0.4$) or AUC of the initial “peak” in salivary UCN-01 ($r^2 = 0.14; P = 0.4$).

Considering that the long terminal decay of UCN-01 in saliva correlated with that in plasma, we questioned whether saliva might also contain AAG. Salivary samples from patients and normal volunteers were analyzed by immunoblotting with detection by a murine monoclonal antibody specific for human AAG; a representative immunoblot is shown in Fig. 2. The multiple bands in saliva most likely represent glycosylation, and the observed sizes of 49 and 55 kDa are consistent with previous reports for human AAG in various biological fluids (25, 26). Based on the intensity of standards, and considering the amount of saliva loaded in each lane, AAG concentrations ranged between 10 and 20 mg/L (200-400 nmol/L) in these two patients (nos. 1 and 2). This concentration of AAG represents at least a 10-fold excess over the concentration of UCN-01 measured in these same samples, suggesting that all UCN-01 in saliva is likely to be bound to AAG.

**Pharmacokinetics of ultrafiltered platinum.** The pharmacokinetics of platinum in plasma ultrafiltrate was consistent with previously reported values for cisplatin given by a 1-hour i.v. infusion (data not shown). Moreover, data from three patients who received a second cycle of treatment showed no apparent difference in platinum disposition between cycle 2 versus cycle 1 (data not shown).

**Tumor biopsy studies.** Six of the seven patients underwent serial tumor biopsies (one patient with thyroid carcinoma was technically biopsiable, but was not biopsied because of concern for her clinical safety; risk of potential airway compromise if post-biopsy bleeding had occurred). Patient 1 underwent serial biopsy with fine-needle aspiration but this did not yield adequate tumor cells to allow analysis. Patients 2 to 6 had malignant melanoma with cutaneous metastases, which facilitated 4 mm punch skin biopsies. The biopsy from patient 2 was uninformative due to spontaneous regression and necrosis of the skin lesion that was biopsied despite having the clinical appearance of a melanoma. Biopsied tumor tissue from patients 3 to 6 were immunohistochemically positive for the melanoma markers MART1 and HMB45 (data not shown). Tumor tissue from patients 4 to 6 were strongly positive for Ki-67 with close to 100% of the tumor cells scored as positive, whereas tumor tissue from patient 3 was $\approx 20\%$ positive for Ki-67 (data not shown). Tumor tissue from patients 3 to 5 were also strongly positive for p53, whereas tumor tissue from patient 6 did not stain for p53; whether this patient is p53 wild-type or null is unknown (data not shown).

Geminin has recently been suggested to be a sensitive marker of cell proliferation (27). Unlike Ki-67 which is expressed at all stages of the cell cycle in proliferating cells, geminin is only expressed in S and G2 phases; it is degraded in mitosis, and does not accumulate again until cells enter the subsequent S phase. The function of geminin is to prevent re-replication of DNA.

Geminin has been used to assess the frequency of cells in S and G2 phase, but it has not previously been applied to the measurement of DNA damage–induced cell cycle perturbation (27). Therefore, we did preliminary experiments in preclinical models to validate geminin as a biomarker for DNA damage–induced cell cycle arrest (Fig. 3). MDA-MB-231 cells were incubated for 24 hours with 0.1 to 10 ng/mL of SN38 (the active metabolite of the topoisomerase I inhibitor irinotecan). The effect of SN38 on these cells has been extensively studied by our laboratory (14, 28, 29). Cells were pelleted, fixed in formalin, sectioned, and analyzed by immunohistochemistry for expression of geminin. Parallel aliquots were analyzed by flow cytometry. Undamaged cells, and those incubated with 0.1 ng/mL of SN38 exhibited similar cell cycle distribution, whereas 56% and 54% of the cells expressed nuclear geminin, respectively (Fig. 3). SN38 at 1 ng/mL caused some accumulation of cells in G2 phase, and 68% of the cells stained positive for geminin. At 10 ng/mL of SN38, the majority of cells arrested in S phase, and 95% of the cells scored positive for geminin. These results show that geminin is readily detectable in cells arrested by DNA-damaging agents.

The expression of geminin was evaluated in tumor biopsies from three patients (nos. 4, 5, and 6); geminin staining for patient 6 is shown in Fig. 4A and the quantitative values for the three patients are shown in Fig. 4B. Prior to treatment, 2% to 8% of the tumor cells showed geminin positivity. Cisplatin treatment consistently increased this value in all three patients, as would be expected if the cells arrested in S or G2 phase. It is notable that this increase, although small, was seen at a cisplatin dose of only 30 mg/m$^2$, well below the standard therapeutic dose range of 75 to 100 mg/m$^2$. All evaluable patients showed a marked decrease in geminin at the conclusion of the 72-hour UCN-01 infusion, consistent with progression of cells into G1 phase of the cell cycle.

Biopsies were also obtained in one patient (no. 6) at the beginning of a second cycle of treatment. Geminin expression in this patient clearly recovered to levels observed before administration of UCN-01, despite the presence of $>10$ μmol/L of UCN-01 in plasma at the start of the second treatment cycle.

**Therapeutic efficacy.** Four out of the seven patients were not evaluated for antitumor effect as they received only one cycle of therapy either because of dose-limiting toxicity ($n = 2$) or clinical disease progression ($n = 2$). Three patients received two

![Fig. 2. Western blot of AAG in saliva from two patients (nos. 1 and 2) and two healthy male volunteers, and concurrently run serial dilutions of pure AAG.](http://example.com/fig_2)
cycles of therapy; all had progressive disease on formal assessment of tumor burden.

Discussion

We observed that cisplatin was clinically tolerated up to doses of at least 30 mg/m² when combined with UCN-01 given at 34 mg/m²/d for 3 days by continuous i.v. infusion. However, unacceptable toxicities were observed in the first two patients (treated on our trial) who received UCN-01 at 45 mg/m²/d for 3 days. This was unexpected, as comparable doses of single-agent UCN-01 were well-tolerated in the NCI phase I trial (15).

Our clinical data are consistent with results obtained in a phase I trial of cisplatin plus UCN-01 conducted by the California Cancer Consortium (24). In that study, dose-limiting atrial fibrillation, azotemia, sepsis, and respiratory failure were seen with cisplatin at 30 mg/m² in combination with UCN-01 at 45 mg/m²/d by 72-hour infusion. In the California trial, UCN-01 doses were not reduced and the study was terminated prior to reaching conventional therapeutic doses of cisplatin. Tumor biopsy specimens were interpretable in two of three patients, and were most consistent with treatment-induced G1 cell cycle arrest. Importantly, biopsies were only obtained pre-cisplatin and post-UCN-01, so it is not possible to determine which drug(s) were responsible for the observed results.

A critical issue, not addressed in prior studies of UCN-01, is whether the drug is bioavailable to tissues given its avid binding to plasma AAG. Our clinical and pharmacokinetic data suggest that at least a component of the early UCN-01 peak in saliva represents free drug in plasma. If this is true, it is notable that UCN-01 concentrations exceeded 7.5 nmol/L—the concentration required to abrogate S phase arrest in preclinical models (14)—in 100% of patients. Of course, drug concentrations in plasma may not necessarily reflect levels achieved in tumors.

Our geminin immunohistochemistry data is the first direct evidence suggesting that concentrations of cisplatin and UCN-01 adequate to modulate cell cycle progression are achieved in human tumors. The timing of biopsies in our patients strongly suggests that UCN-01, and not cisplatin, was responsible for decreased geminin expression. It is not currently possible to determine whether this response is due to the abrogation of S/G2 arrest or the induction of G1 arrest. G1 arrest occurs in vitro when cancer cells are exposed to >100 nmol/L UCN-01, whereas <10 nmol/L inhibits Chk1 and abrogates cell cycle arrest (14). Importantly, the geminin data strongly suggest that pharmacologically active UCN-01 is available to tissues over the time frame of the drug infusion. Taken together, the salivary and geminin data suggest that concentrations of UCN-01 adequate to inhibit cell cycle checkpoints can be safely achieved in combination with cisplatin—even at 75% of the UCN-01 single-agent MTD. Future trials of combination regimens UCN-01 should therefore consider doses at or below 75% of the single-agent MTD—a tolerable dose that apparently achieves adequate drug concentrations in tumors.

The geminin data also suggest that persistent UCN-01 in plasma may not antagonize the effects of cytotoxic drugs—by inducing G1 arrest—in subsequent cycles. This has been a potential concern for the use of UCN-01 in combination with cytotoxic agents, given its prolonged elimination kinetics. This concern is highlighted by the observed accumulation of cells in G1 by the end of the first cycle of UCN-01. However, persistent UCN-01 in plasma is probably not pharmacologically active. In patient no. 6, recovery of geminin immunohistochemistry staining at the start of cycle 2 occurred despite the presence of >10 µmol/L UCN-01 in plasma. This suggests that tissue concentrations of UCN-01 at that time were below the threshold to induce G1 arrest, consistent with the very low concentrations of UCN-01 seen in saliva at that time.

Our trial concluded prior to fully testing the original hypothesis regarding cell cycle modulation, and before reaching MTD. Dose titration was discontinued because an inpatient 72-hour infusion does not seem to be practical in regular oncologic practice, as it is not very acceptable to patients. While our study was under way, other studies defined the MTD for
single-agent UCN-01 by 3 hours of i.v. infusion (16, 17). Therefore, we continue to test our original hypothesis in a recently opened study, using a 3-hour outpatient i.v. infusion of UCN-01 (at 75% of the single-agent MTD) in combination with cisplatin. Dose titration is ongoing, but we have now safely treated two patients at full therapeutic single-agent cisplatin doses (75 mg/m²); full details of this study, including pharmacokinetics and molecular pharmacodynamics, will be reported separately once the trial is completed.

In conclusion, cisplatin may be given safely up to doses of at least 30 mg/m² in combination with UCN-01 at 34 mg/m²/d for 3 days of infusion (75% of the single-agent MTD). Salivary UCN-01 pharmacokinetics and geminin immunohistochemistry results strongly suggest that UCN-01 concentrations adequate to modulate cell cycle checkpoints can be safely achieved in human tumors. These findings have been incorporated into the design of a revised study to test the hypothesis that clinically tolerable doses of UCN-01, by 3 hours of infusion, abrogate cell cycle arrest induced by therapeutic doses of cisplatin.

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