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ORIGINAL REPORT

Safety and Pharmacokinetics of Escalated Doses of Weekly Intravenous Infusion of CCI-779, a Novel mTOR Inhibitor, in Patients With Cancer

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
To establish the safety, tolerability, and pharmacokinetic parameters of CCI-779, a selective inhibitor of the mammalian target of rapamycin, in patients with advanced cancer.

Patients and Methods
Using a modified continuous reassessment method, we performed a phase I with pharmacokinetic study of CCI-779 given as a weekly 30 minutes intravenous (IV) infusion.

Results
Twenty-four patients received CCI-779 at doses ranging 7.5 to 220 mg/m^2. No immunosuppressive effect was reported. Dose-limiting thrombocytopenia occurred in two patients at 34 or 45 mg/m^2. At 220 mg/m^2, dose-limiting toxicities consisted of manic-depressive syndrome, stomatitis, and asthenia in two of nine patients, preventing further dose escalation. The most frequent drug-related toxicities were acne-like, maculopapular rashes and mucositis or stomatitis. All toxicities were reversible on treatment discontinuation. Maximum concentration and area under the concentration-time curve increase subproportionally with dose. Mean steady-state volume of distribution ranged from 127 to 385L. Sirolimus was a major metabolite (metabolite-to-parent ratio range, 2.5 to 3.5). Whole blood clearance was nonlinear, ranging from 19 to 51 L/h (34 to 220 mg/m^2). Variability predicted with flat doses appears comparable with data based on body-surface area–normalized treatment. Partial responses were observed in one patient with renal clear-cell carcinoma and in one patient with breast adenocarcinoma.

Conclusion
CCI-779 displayed no immunosuppressive effects with manageable and reversible adverse events at doses up to 220 mg/m^2, the highest dose tested. Based on our results, weekly doses of 25, 75, and 250 mg CCI-779 not based on classical definitions of maximum-tolerated dose are being tested in phase II trials in patients with breast and renal cancer.

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INTRODUCTION

The mammalian target of rapamycin (mTOR), a member of the phosphatidyl inositol 3' kinase family, is a multifunctional serine-threonine kinase that acts as central regulator of cell growth, proliferation, and apoptosis.[1-4] mTOR is activated in response to growth stimuli such as nutrients and/or growth factors including insulin, insulin growth factor, platelet-derived growth factor, and the stem-cell factor.[1,2,5] Stimulation of mTOR results in a series of events involving phosphorylation of translational regulation factors such as eukaryotic initiation factor 4E-binding protein and p70^{s6} kinase.[6,7]

Rapamycin (sirolimus), an immunosuppressant macrolide produced by *Streptomyces hygroscopicus*, binds FKBP-12 (FK506 binding protein), creating a molecular complex that specifically inhibits mTOR functions.[8] Inhibition of mTOR by rapamycin leads to downregulation of G1 cyclin/cdk complexes and p27 accumulation that blocks progression in late G1/S phase of cell cycle.[9,10] In addition to immunosuppres-

sion, sirolimus is thought to retard proliferation of endothelial and vascular smooth muscle cells required for tumor angiogenesis.[11] Recently, studies showed that sirolimus also inhibited the oncogenic transformation of human cells induced by either PI3K or AKT in mice with loss of the normal *PTEN* allele (*PTEN*$^{\pm}$).[12-14] Sirolimus can also induce apoptosis and sensitize cancer cells to apoptosis induction by DNA-damaging agents such as cisplatin.[15] In humans, sirolimus was usually well tolerated at daily doses ranging 0.5 to 60 mg/d; hypercholesterolemia, hypertriglyceridemia, lymphopenia, thrombocytopenia, mucositis, arthralgia, and infection are the main toxicities.[16]

CCI-779 (Fig 1), a water-soluble ester of sirolimus,[9-17] was identified by the Developmental Therapeutic Branch of the National Cancer Institute as a noncytotoxic agent that delayed tumor proliferation.[18] At several nontoxic doses, CCI-779 demonstrated antitumor activity in a variety of human cancer models, such as gliomas; rhabdomyosarcoma; primitive neuroectodermal tumor, such as medulloblastoma; and prostate and breast cancer.[19-23] Treatment of mice with CCI-779 normalizes $p70^{s6}$ kinase activity and reduces neoplastic proliferation. As with sirolimus, *PTEN*-deficient human tumors are more sensitive to CCI-779-mediated growth inhibition than *PTEN*-expressing cells.[12,14,24] Interestingly, preclinical studies indicate that intermittent administration of CCI-779 reduces its immunosuppressive properties while retaining its antitumor activity (CCI-779 investigator brochure).

Based on the promising antitumor activity and safety data showing limited immunosuppression with intermittent exposure to CCI-779 in animals, this phase I dose-escalation study was undertaken to determine the safety, basic pharmacokinetic characteristics, and preliminary antitumor effects of weekly intravenous (IV) infusion of CCI-779 in patients with advanced malignancies.

PATIENTS AND METHODS

Patient Selection

Patients entered onto this study met the following criteria: histologically confirmed diagnosis of solid tumor refractory to standard therapy or for whom no standard therapy existed; age $\geq$ 18 years; life expectancy $\geq$ 3 months; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2; no chemotherapy, hormonal therapy, immunotherapy or radiotherapy within 4 weeks before treatment with CCI-779 (6 weeks for previous treatment with nitrosoureas, mitomycin, or extensive radiotherapy) and no immunosuppressive agents within 3 weeks before study entry (except corticosteroids used as antiemetics); adequate hepatic function defined as serum bilirubin less than 25 μmol/L ($<$ 1.5 mg/dL), transaminases $\leq$ 3.0 times the upper limit of normal (or $\leq$ 5 in the case of liver metastases); adequate bone marrow function defined as absolute neutrophil count $>$ 1,500/μL, platelets $>$ 100,000/μL, and hemoglobin $>$ 8.0 g/dL; adequate renal function with serum creatinine less than 2.0 mg/dL) and/or creatinine clearance (Cockroft formula) $\geq$ 60 mL/min; baseline cholesterol $<$ 350 mg/dL, triglycerides $<$ 300 mg/dL, no history of alcoholism, drug addiction, or psychotic disorders; no medical condition which, in the opinion of the investigator, was incompatible with the protocol; no uncontrolled systemic infection; and signed informed consent according to institutional and national guidelines.

Patients were excluded if they were pregnant or breast feeding, had symptomatic brain metastases or leptomeningeal tumor involvement, active infection or serious intercurrent illness, known hypersensitivity to macrolide antibiotics, or were receiving any of the following: concomitant antitumor therapy, anticonvulsant therapy, or cardiac antiarrhythmic drugs. Patients were not required to have evaluable or measurable disease.

Based on known toxicities of rapamycin, patients entered onto this trial were also required to have baseline serum cholesterol $<$ 350 mg/dL, triglycerides $<$ 300 mg/dL, no immunosuppressive agents within 3 weeks before study entry (except corticosteroids used as antiemetics), and no known concomitant genetic or acquired immunosuppressive diseases (such as AIDS).

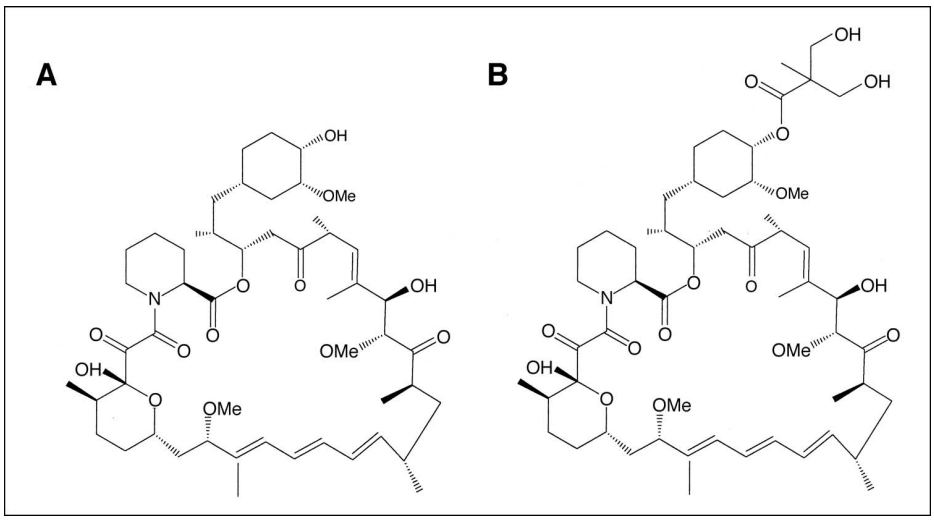

Fig 1. Chemical formula of sirolimus (A) and CCI-779 (B).

Pretreatment and Follow-Up Examinations

Complete medical history, physical examination, ECOG performance status, and biochemical profile including cholesterol, triglycerides, full blood count and urinalysis were performed at baseline and repeated weekly (twice weekly for blood count). A 12-lead electrocardiogram and a chest x-ray were obtained within 14 days before administration of CCI-779 and repeated every 4 weeks. Toxicity was evaluated by weekly clinical and laboratory examination and graded using the National Cancer Institute Common Toxicity Criteria, version 2.0.[19] Additional laboratory tests and/or an increase in the frequency of observations were permitted to document acute drug-related toxicity until recovery.

Total serum testosterone, follicle stimulating hormone, and luteinizing hormone were determined in males at baseline and every 4 weeks. A serum pregnancy test was performed in females of childbearing potential. Lymphocyte subsets CD45, CD14, CD3, CD4, CD8, and CD56 and mitogen proliferation assays were done in the prestudy period, before the first three infusions, and then every 2 months.Tumors were measured by computed tomography scans 4 weeks before starting CCI-779 and then every 8 weeks.

Drug Administration

CCI-779 (Wyeth Pharmaceuticals, Collegeville, PA) was supplied in concentrated form in sterile, 1mL or 5mL glass ampules (containing 25 mg CCI-779/mL 100% ethanol). Before each CCI-779 administration, the patient's body-surface area (BSA) was recalculated from height and weight. Study drug was administered once weekly as a 30-minute IV infusion after pretreatment with IV antihistamine with close monitoring during and for at least 2 hours after the end of CCI-779 infusion.

Dose-Escalation Procedure

Based on animal toxicology data and prior clinical experience with sirolimus, the starting dose was 7.5 mg/m^2. This study was designed with no prefixed dose levels. A modified continual reassessment method was used to generate a new estimate of the maximum-tolerated dose (MTD) using a Bayesian approach after each patient had completed three infusions.[25,26] The MTD was defined as the dose level at which $\geq$ 33% of the patients would experience dose-limiting toxicity (DLT). DLT was defined as $\geq$ grade 3 nonhematological toxicity (excluding alopecia, untreated nausea and vomiting, and/or serum triglycerides if $<$ 1,500 mg/dL and recovered within 1 week), grade 4 thrombocytopenia, grade 4 neutropenia lasting $>$ 5 days, grade 4 febrile neutropenia requiring hospitalization, or treatment delay of $>$ 2 weeks as a result of unresolved toxicity.

Additional rules were applied to determine the proportion by which the dose was escalated or reduced. If grade $\leq$ 1 toxicity occurred, then the dose could be escalated by $\leq$ 100% (maximum of two times the previous dose); if grade 2 toxicity occurred, then the dose could be escalated by $\leq$ 50%; if grade 3 thrombocytopenia or grade 3 to 4 nonfebrile neutropenia lasting $\leq$ 5 days occurred (no hospitalization and no treatment delay $>$ 2 weeks), then the dose could be escalated by up to 33%. If DLT occurred, then the dose was decreased by up to 33%.

Infusions could be delayed for less than 2 weeks for the patient to recover from toxicities. No intrapatient dose escalation was allowed. Dose reduction of 0% to 33% was allowed in response to unacceptable toxicity if the patient exhibited evidence of clinical benefit from CCI-779. If unacceptable toxicity occurred after this dose reduction, the patient was no longer allowed to take CCI-779 at any dose level. These reduced doses were not included in the MTD calculations.

Bioanalytic Method

Blood samples (3 mL each) for determination of CCI-779 and sirolimus in sodium EDTA-anticoagulated whole blood were collected before treatment and at 0.25, 0.5 (end of infusion), 1, 2, 4, 6, 24, 48, 72, 96, and 168 hours (before the next weekly treatment) following the start of infusion during the first and fourth doses. In addition, 10 mL of blood for plasma was obtained at 0.5 (end of infusion), 72 and 168 hours during the first dose, and if possible, during the fourth dose of CCI-779.

CCI-779 and sirolimus concentrations in whole blood were validated from 0.25 to 100 ng/mL (CCI-779) and from 0.1 to 100 ng/mL (sirolimus) using separate, slightly differing methods (Taylor Technology Inc, Princeton, NJ). Briefly, to 0.1 mL of methanol was added an aliquot of d_7-CCI-779 or 32-desmethoxyrapamycin internal standard. The spiked mixtures were added to 1 mL of whole blood treated with sodium EDTA. Analytes were extracted into 1-chlorobutane, evaporated, reconstituted with a 70:30 methanol:water solution, and chromatographed using either a C18 column (for CCI-779) or C4 column (for sirolimus) with a gradient of methanol and water containing ammonium acetate and acetic acid as the mobile phase solvents. The analytes were detected and quantified by tandem mass spectrometry using atmospheric pressure chemical ionization.

CCI-779 concentrations in plasma were validated from 0.25 to 100 ng/mL. To 0.1 mL of methanol was added an aliquot of d_7-CCI-779 internal standard. The spiked mixture was then added to 1 mL of plasma. Analytes were extracted into *tert*-butyl methyl ether and analyzed as described previously. These methods exhibit adequate inter- and intrasubject variability ($\leq$ 12.7%) and bias ($\leq$ 15%). CCI-779 and sirolimus concentrations in whole blood were stable following several freeze-thaw cycles, brief incubations at room temperature, and long-term storage at $-$80°C.

Pharmacokinetic Analyses

The concentration-versus-time data for CCI-779 and sirolimus in whole blood were analyzed using a noncompartmental analysis technique.[27] Pharmacokinetic analysis is based on concentrations measured in whole blood due to the limited stability of CCI-779 and sirolimus in plasma. Calculated were peak concentration (C_{max}), half-life ($t_{1/2}$), area under the concentration-time curve (AUC_t), clearance (Cl), and steady-state volume of distribution (Vd_{ss}). An accumulation ratio (AR) was determined by taking the ratio of AUC_t on week 4 to AUC_t on week 1. In addition, the ratio of sirolimus to CCI-779 AUC (AUC_{SIR}/AUC_{CCI}) and the sum of CCI-779 plus sirolimus AUCs (AUC_{sum}) were calculated (unadjusted for modest differences in molecular weight). To preliminarily assess the proportionality of exposure with dose, an exponential regression model was used to describe the relationship between CCI-779 C_{max}, AUC, and AUC_{sum} versus dose.[28]

RESULTS

General

A total of 24 patients were enrolled onto the study and received at least one cycle (four weekly doses) of CCI-779 at doses of 7.5 to 220 mg/m^2. A total of 273 infusions were administered. Patient characteristics at study entry are summarized in Table 1. Dose escalation was based on acute

Table 1. Patient Characteristics (N = 24)

	No. of Patients
Sex	
Male	14
Female	10
Age, years	
Median	54
Range	30-63
ECOG performance status	
0	10
1	10
2	4
Primary tumor type	
Renal	6
Colorectal	4
Soft tissue sarcoma	3
Mesothelioma	2
NSCLC	2
Adrenocortical carcinoma	1
Breast	1
Head and neck, squamous cell	1
Melanoma	1
Neuroendocrine carcinoma	1
Pancreatic	1
Prostate	1
Prior therapy	
Chemotherapy alone	24
Surgery	19
Chemotherapy and radiotherapy	12
No. of prior chemotherapy regimens	
1	5
2	8
3	3
≥ 4	8

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small-cell lung cancer.

toxicity evaluated during the first four infusions of CCI-779. As shown on Table 2, no grade 3 to 4 toxicity was observed up to the dose of 22.5 mg/m^2. At a dose of 34 mg/m^2, one patient developed a grade 3 neutropenia, thrombocytopenia, and hypophosphatemia. Bone marrow aspiration found no megacaryocyte. This patient had previously received extensive radiation therapy that could have participated to CCI-779 hematologic toxicity. This event led us to enter two additional patients at the dose level of 34 mg/m^2 without further evidence of severe toxicity. Therefore, the dose escalation was resumed. At a dose of 45 mg/m^2, one patient had grade 3 thrombocytopenia, asthenia, and diarrhea. Three additional patients were entered at this dose level without additional DLT. Dose escalation continued without additional DLT up to 220 mg/m^2. At the 220 mg/m^2 dose-level, a 51-year-old woman with metastatic breast cancer and no history of psychiatric disorders developed grade 2 euphoria and insomnia after 2 weeks of treatment. At week 4, the patient was hospitalized for grade 3 depression and received antidepressive treatment with paraxetine and cyanemazine (no evidence of brain and leptomeningeal metastasis); grade 3 stomatitis; and grade 3 transaminases elevation. The toxicity was reversible within 2 weeks of treatment discontinuation. The patient was subsequently restarted at a dose of 165 mg/m^2 without further evidence of psychiatric disorder. At the 220 mg/m^2 dose level, two additional patients without prior neuropsychiatric disorder developed reversible grade 1 to 2 depression preceded by grade 1 to 2 euphoria. Among subsequent patients entered at this dose level, one developed DLTs that consisted of grade 3 asthenia and grade 3 stomatitis. Therefore, although the formal definition of MTD was not met, it was decided to stop the dose escalation.

Safety and Tolerability After Repeated Cycles

Tables 3 and 4 summarize drug-related toxicities observed with a total frequency of ≥ 20% during this study. No immunosuppressive effects were detected during treatment with CCI-779. For example, in eight patients treated at the highest tested doses, the median changes (± standard deviation [SD]) from the pretreatment value for lymphocytes (all CD45+) including CD14+, CD3+, CD58+/CD3−, CD56+/CD3+, CD4+/CD3+, and CD8+/CD3+

Table 2. Grade 3-4 and Dose-Limiting Toxicities During First Month of Treatment With CCI-779

Dose (mg/m^2)	No. of Patients	Grade 3-4 Toxicity	Type of Toxicity and Grade
7.5	1	—	—
15.0	2	—	—
22.5	1	—	—
34.0	3	1	—
45.0	4	1	One patient with grade 3 neutropenia, thrombocytopenia, and hypophosphatemia; one patient with grade 3 thrombocytopenia, asthenia, and diarrhea
60.0	1	—	—
80.0	1	—	—
110.0	1	—	—
165.0	1	—	—
220.0	9	2	One patient with grade 3 manic-depressive syndrome with grade 3 stomatitis, and grade 3 ALT elevation; one patient with grade 3 asthenia and stomatitis

Table 3. Drug-Related Toxicities With Total Frequencies ≥ 20% After Repeated Dosing of CCI-779*

	Intermediate Doses (7.5-165.0 mg/m^2) (n = 15)	Highest Dose (220 mg/m^2) (n = 9)	No. of Patients	%
Dermatologic				
Grade 1-2	12	5	17	71
Grade 3-4	1	—	1	4
Mucositis				
Grade 1-2	10	7	17	71
Grade 3-4	—	1	1	4
Asthenia				
Grade 1-2	7	2	9	38
Grade 3-4	1	1	2	8
Nausea				
Grade 1-2	5	5	10	42
Grade 3-4	—	—	—	—
Thrombocytopenia				
Grade 1-2	4	1	5	21
Grade 3-4	2	—	2	8
Anorexia				
Grade 1-2	3	2	5	21
Grade 3-4	—	—	—	—
Diarrhea				
Grade 1-2	3	1	4	17
Grade 3-4	1	—	1	4
Vomiting				
Grade 1-2	2	3	5	21
Grade 3-4	—	—	—	—
Hypercholesterolemia				
Grade 1-2	—	—	—	—
Grade 3-4	3	2	5	21
Hypertriglyceridemia				
Grade 1-2	2	—	2	8
Grade 3-4	2	1	3	13
Peripheral edema				
Grade 1-2	3	2	5	21
Grade 3-4	—	—	—	—
Weight loss				
Grade 1-2	3	2	5	21
Grade 3-4	—	—	—	—
Taste perversion				
Grade 1-2	3	2	5	21
Grade 3-4	—	—	—	—

*No grade 3 or 4 drug-related adverse event was reported at the doses of 22.5, 60, 110, and 165 mg/m^2.

were 6.5% (SD, 6.4%), −3.1% (SD, 7.8%), −1.4% (SD, 6.5%), 0.07% (SD, 0.6%), 0.2% (SD, 5.5%), and −0.2% (SD, 1.7%), respectively. Likewise, large interpatient variability in mitogene proliferation assay was observed with a 4.5% (SD, 37%) increase in median values of concanavaline A after 1 month of treatment ($P > .5$). Thrombocytopenia was grade 1 to 2 in five patients and grade 3 to 4 in two patients. Asthenia was grade 1 to 2 in nine patients and grade 3 in two patients.

The most frequent drug-related adverse events were dermatologic toxicities and mucositis/stomatitis (18 of 24 patients; Table 3). Stomatitis consisted mainly of 1 to 3 round grade 1 to 2 aphtous lesions in the mouth and tongue. Stomatitis was severe (grade 3) in only one of nine patients treated at the highest dose and was reversible despite treatment continuation. Antiseptic mouthwashes were inconsistently effective in preventing stomatitis.

Specific dermatologic toxicities are presented in Table 4. Skin toxicity consisted of grade 1 to 2 herpes simplex lesions (five patients; Fig 2A), acne-like rash (nine patients; Fig 2B), maculopapular rash (12 patients; Fig 2C), dry skin (nine patients), pruritus (seven patients), and nail disorders (11 patients; Fig 2D).

Herpes lesions were documented using viral cultures and both topic and systemic treatments with acyclovir were given to patients with herpetic lesions. Maculopapular rashes, generally consisting of 5 to 10 cm reactions on face and neck, mainly occurred during the first few weeks of treatment and were spontaneously reversible. Grade 1 to 2 acne-like rash on erythematous base occurred on the face and the upper part of the trunk. Histopathologic examination revealed a nonspecific accumulation of neutrophils in dermis and epidermis. This skin reaction was reversible with and without topical steroid cream.

Grade 3 elevations of total cholesterol and triglycerides were observed in five and three patients, respectively, across the range of doses explored. Three patients had grade 1 to 2 and one patient had grade 3 ALT elevations. Among 11 males who had normal baseline testosterone levels, nine showed reduction of these levels with increased follicle-stimulating hormone and/or luteinizing hormone levels during CCI-779 treatment. At doses of 15 and 45 mg/m^2, two patients reported reduced sexual activity (considered grade 2).

Pharmacokinetic Results

Typical pharmacokinetic profiles of CCI-779 and its main metabolite sirolimus are displayed in Figure 3. Mean pharmacokinetic parameters are presented in Tables 5 and 6.

Following treatment, CCI-779 decreased in a polyexponential manner. AUC increased proportionally with doses up to 150 mg. Doses higher than 300 mg CCI-779 yielded high AUCs and low clearance in some patients. Thus, the interpatient variability made difficult to assess the linearity of AUC with doses greater than 300 mg (Fig 4). CCI-779 did not exhibit preferential partitioning into RBCs, and yielded mean end-of-infusion blood/plasma ratio values of 0.64-1.15 (Coefficient of variation [CV]: 17% to 68%). Mean steady-state volume of distribution was large with mean values of 127 to 384 L (CV, 7% to 44%). Interestingly, Vd_{ss} appeared to exhibit an inverted U-shaped profile throughout the dose range, suggestive of saturable drug distribution at very high doses. Clearance of CCI-779 from whole blood increased with increasing dose with mean values ranging 19 to 51 L/h (CV, 14% to 32%). Two-way analysis of variance showed that doses significantly affected the Clearance of CCI-779 ($P < .001$). Mean

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