CCI-779 in Metastatic Melanoma

A Phase II Trial of the California Cancer Consortium

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BACKGROUND. CCI-779 is an analog of the immunosuppressive agent, rapamycin, that has demonstrated activity against melanoma in preclinical models and shown clinical benefit in patients with breast and renal carcinoma. CCI-779 is not immunosuppressive when administered on an intermittent schedule, and its toxicity is modest, consisting of nausea, diarrhea, hypertriglyceridemia, thrombocytopenia, asthenia, and follicular dermatitis.

METHODS. The current trial was designed to detect a median time to disease progression of >18 weeks in patients with metastatic melanoma treated with a 250-mg weekly dose of CCI-779 administered intravenously after diphenhydramine premedication. Patients with measurable disease, no more than one previous chemotherapy regimen for metastatic disease, and normal organ function were eligible, and patients with central nervous system involvement, P450-inducing or P450-suppressing drugs, or hypertriglyceridemia were excluded.

RESULTS. Thirty-three patients (21 males) were treated, 21 of whom had been treated previously with chemotherapy and/or biologic agents for advanced-stage disease. One patient had a partial response lasting 2 months. The median time to disease progression and overall survival were 10 weeks and 5 months, respectively. Toxicity was mild and predominantly mucocutaneous (stomatitis, diarrhea, and rash). Hyperlipidemia was cumulative and was managed with lipid-lowering agents.

CONCLUSIONS. CCI-779 was not sufficiently active in melanoma to warrant further testing as a single agent. ***Cancer* 2005;104:1045–8.**

KEYWORDS: CCI-779, rapamycin analog, metastatic melanoma.

CCI-779 mTOR kinase inhibitor is an ester derivative of sirolimus (rapamycin), which was formulated for intravenous use. Drugs of this class inhibit cell cycle progression by binding to FK506-binding protein-12 (FKBP12) to form a complex that interacts with the "mammalian target of rapamycin" (mTOR), resulting in inhibition of signal transduction pathways required for progression through the cell cycle.[1] Perturbation of these pathways, downstream of protein kinase B (PKB/AKT)/phosphoinositol-3-kinase (PI3K) activities, results from upstream mutations, that are mutated in human cancers, most commonly loss of the PTEN (phosphatase and tensin homolog deleted on chromosome 10) tumor suppressor, which leads to overexpression of AKT or PI3K resulting in mTOR overexpression. PTEN mutations are found in approximately one-half of melanomas.[2] The resulting increase in the activity of mTOR is believed to "uncouple" it from the normal control exerted on its activity by the availability of nutrients required for cell proliferation.[3]

The CCI-779–FKBP12 complex inhibits the mTOR kinase activity

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of ribosomal subunits responsible for the translation of selected mRNAs into proteins required for progression from the G_1 to the S phase of the cell cycle. Although the prototype agent, rapamycin, is used as an immunosuppressive due to its inhibition of interleukin-2 (IL-2)–induced signaling activities in T lymphocytes, related agents such as CCI-779 that inhibit malignant cell cycling by this mechanism are not immunosuppressive at doses and schedules associated with antitumor activity.[4] The preclinical investigation of CCI-779 demonstrated that prostate, breast, leukemia, and melanoma cell lines could be inhibited by CCI-779, and animal models confirmed its activity in human lymphoma, glioblastoma, melanoma, colon, breast, pancreatic, and prostate carcinoma.[4–6] The intermittent dosing schedule was associated with antitumor activity but only transient immunosuppression.

In Phase I clinical trials, the dose-limiting toxicities included myelosuppression, diarrhea, stomatitis, fever, fatigue, and hyperlipidemia. Skin reactions were common, ranging from dry desquamation to eczematoid, urticarial, and acneiform rash. Acute infusion reactions resembled histamine-release phenomena and have been avoided by premedication with antihistamines[7,8] (and unpublished data). Based on these safety data as well as pharmacokinetic and pharmacodynamic results, a fixed dose of 250 mg was proposed for evaluation on a weekly dosing schedule in patients with advanced melanoma. Because the mechanism of action may be associated with cytostatic rather than cytotoxic effects on tumor cells, the primary objective of this Phase II trial was to detect a median progression-free interval of $\geq$ 18 weeks among patients with advanced melanoma who had received at most 1 previous therapy regimen for metastatic disease.

MATERIALS AND METHODS

Patient Eligibility Criteria

The protocol was conducted by the California Cancer Consortium (City of Hope Comprehensive Cancer Center, University of Southern California-Kenneth Norris Cancer Center, and University of California at Davis Cancer Center), the Princess Margaret Hospital, and the University of Chicago, and approved by the institutional review board at each participating institution. Written, voluntary informed consent was obtained from all patients before initiating any protocol procedures. Patient eligibility criteria included the following: measurable metastatic or locally advanced melanoma, age $\geq$ 18 years, life expectancy $\geq$ 4 months, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2, leukocyte count $\geq 3000/\mu L$, absolute neutrophil count $\geq 1500/\mu L$, platelet count $\geq 100{,}000/\mu L$, serum bilirubin and creatinine levels within institutional normal limits (or creatinine clearance $\geq$ 60 mL/min), and transaminase level $<$ 2.5 times the upper limit of institutional normal. Serum cholesterol level was required to be $<$ 350 m/dL and triglyceride level was required to be $<$ 300 mg/dL, which could be achieved with lipid-lowering agents. Patients were permitted to have received up to one chemotherapy-containing regimen given adjuvantly and up to one chemotherapy-containing regimen for advanced-stage disease (no previous chemotherapy for advanced-stage disease if disease recurrence occurred within 6 months of adjuvant chemotherapy). Patients with any history of central nervous system metastasis were excluded, as were patients with human immunodeficiency virus infection or ongoing steroid therapy, patients requiring full anticoagulation for previous thromboembolic disease, or patients requiring any of the excluded concomitant therapies, which consisted of a number of agents known to significantly induce or suppress cytochrome P450-3A.

Therapy and Monitoring

CCI-779 was administered as a fixed weekly intravenous dose of 250 mg. All patients were premedicated with diphenhydramine 25 or 50 mg intravenously, and the CCI-779 was then infused over 30 minutes. For any patient experiencing an acute hypersensitivity reaction (urticaria, bronchospasm or dyspnea, hypotension), the infusion was stopped, additional H1 and H2 antihistamines were administered, and infusion was resumed at a slower rate after resolution of the reaction. Patients were generally also premedicated with standard antiemetics including modest doses of dexamethasone and 5HT-3 blockers.

Patients were monitored for toxicity with a weekly complete blood count and comprehensive metabolic panel and fasting lipid panel. The National Cancer Institute-Common Toxicity Criteria version 2.0 was used for toxicity grading. For patients whose serum triglyceride level was $>$ 500 mg/dL, lipid-lowering therapy was instituted and CCI-779 was withheld until the level was $<$ 500 mg/dL. Dose delays and adjustments for other noninfusion-related toxicities provided for approximately 30% dose decrements after recovery of toxicity or a $\leq$ 2-weeks delay to allow resolution of toxicity.

Tumor assessments were performed every 8 weeks, using the same modality that had been used for initial measurements. For patients experiencing a complete or partial response, a confirmatory assessment was to be done 4 weeks after the first response-defining assessment.

Statistical Analysis

The primary end point of the study was the percentage of patients surviving progression free at 18 weeks. Objective response and survival were the secondary end points. The assumptions regarding disease progression-free survival (PFS) were based on unpublished data from the Southwest Oncology Group database (J. Moon, personal communication), in which the median overall survival period is 7–9 months and the median time to disease progression is approximately 3 months for patients with advanced-stage melanoma enrolled in clinical trials. Thus, for the purpose of the current study, a meaningful PFS of 4.5 months, a 50% increase over the natural history of this disease, was selected.

The 1-stage design provided a maximum of 45 patients and an interim analysis after 22 patients were assessable for the primary end point, allowing continued accrual during the interval required to assess all 22 patients. Among the first 22 patients, if $\geq$ 16 patients developed progressive disease before 18 weeks, the probability that the median PFS would be $>$ 18 weeks was $<$ 30%. Because accrual was allowed to continue during the required follow-up time for the first 22 patients, the final accrual to this protocol was 33 patients.

RESULTS

Thirty-three eligible and evaluable patients were enrolled between June 2001 and September 2003. The demographic and disease-related data are provided in Table 1. Twenty-one patients were male, the median age of the patients was 59 years (range, 27–83 years), most patients had an ECOG performance score of 0 or 1, and 21 patients had received previous chemotherapy for advanced-stage disease. Twelve patients had sites of metastatic disease that included the liver. The median PFS was 10 weeks (range, 3–36 weeks) and the median overall survival was 5 months. The median time on protocol therapy was 10 weeks (range, 4–36 weeks). One patient experienced a partial response lasting 2 months. All of the other patients experienced disease progression during protocol therapy.

The toxic side effects of therapy were mild to moderate and are listed in Table 2. Treatment-related fatigue that abated with discontinuation of therapy was common, but never severe. Mucocutaneous toxicity was common, but rarely required a dose adjustment. The other toxicities requiring treatment dose adjustment or delay generally consisted of mucocutaneous symptoms (stomatitis, diarrhea, follicular dermatitis) and/or myelosuppression. No patient died of treatment toxicity, and there were no episodes of neutropenic infection.

TABLE 1
Patient Characteristics

Characteristics	No. of patients
Median age (range) (yrs)	59 (27–83)
Gender	
Male	21
Female	12
ECOG performance status	
0	17
1	10
2	2
M classification	
1a	1
1b	8
1c	24
Lactate dehydrogenase level	
Normal	20
Elevated	13
Previous systemic therapy	
IFN-α, interleukin-2, or both	14
Combination chemotherapy, biotherapy, or both	8
Single-agent chemotherapy	3
Levamisole	1
Tamoxifen	1

yrs: years; ECOG: Eastern Cooperative Oncology Group; IFN-α: interferon-alpha.

TABLE 2
Toxicities of Protocol Therapy

System	Grade 1	Grade 2	Grade 3
Mucocutaneous			
Rash	19	5	1
Stomatitis	26	3	
Diarrhea	6		2
Hematologic			
Neutropenia	5	2	
Thrombocytopenia	21	3	
Endocrine/metabolic			
Hypertriglyceridemia	21	4	
Hypercholesterolemia	15	10	

DISCUSSION

The results of our clinical trial demonstrated that CCI-779 given at the dose and schedule supported by Phase I and pharmacodynamic studies did not have sufficient antitumor activity in melanoma to warrant further evaluation as a single agent. Although the possibility of therapeutic synergism requires further investigation, the spectrum of toxicities associated with this agent overlaps with those of several other drugs in routine use, which limits the choices of combinations that could be safely considered. Currently, very little data exist regarding the clinical or even preclinical experience of CCI-779 in combinations. A preliminary report in 2003 details the results of a Phase I dose-

escalation study that combined CCI-779 with interferon-alpha (IFN-α) at a low dose, which could be escalated in the individual patient if no dose-limiting toxicity of CCI-779 occurred. In that study,[9] even very low doses of CCI-779 (the highest dose reported was 25 mg weekly) in combination with IFN-α (starting at 6 million U subcutaneously 3 times per week) resulted in a high frequency of mucositis, nausea, fatigue, and hyperlipidemia. Two of the first 20 patients were reported to have experienced a partial response. The authors concluded that the combination was well tolerated and potentially active, with mechanisms of action that included both direct antitumor activity and antiangiogenic effects.[9] The study design of our trial did not allow us to distinguish between the possibility that the dose and selected schedule did not provide adequate inhibition of mTOR pathways, or to determine whether there were other mechanisms in the biology of melanoma that allowed this pathway to be bypassed as a mechanism of resistance. There remains some uncertainty about the optimal dose of this drug to be administered on a weekly schedule, which would be of importance in designing studies for diseases that may be more sensitive to the inhibition of this pathway.

As a single agent in the treatment of patients with other diseases, CCI-779 has been more promising and is currently undergoing evaluation in Phase III trials. In a Phase II trial comprising 109 patients with advanced-stage breast carcinoma, approximately one-half of the patients previously exposed to anthracycline and/or taxane experienced an objective response or stable disease lasting $\geq$ 8 weeks when treated with CCI-779 at a dose of 75 or 250 mg weekly.[10] In a similar study testing 3 different dose levels of CCI-779 (25, 75, or 250 mg weekly), a comparable level of activity was observed among 110 patients with advanced-stage renal carcinoma,[11] an encouraging result that undoubtedly will be applied to the design of future Phase III trials to compare or combine other promising new agents with CCI-779 in patients with advanced-stage renal carcinoma.Elucidation of the therapeutic mechanisms of antitumor activity for CCI-779 and other mTOR inhibitors has led to an increased understanding of the mechanisms of resistance, which include mutations in mTOR, FKBP12, or any of the many others associated with mTOR-related pathways.[12] The optimal use of this class of agents in malignancy will await the design of regimens that take into account the need for nonoverlapping clinical toxicities and complementary antitumor mechanisms that minimize the emergence of resistant clones.

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