A Phase I and Pharmacokinetic Study of Temsirolimus (CCI-779) Administered Intravenously Daily for 5 Days Every 2 Weeks to Patients with Advanced Cancer

Manuel Hidalgo,[1,2] Jan C. Buckner,[3] Charles Erlichman,[3] Marilyn S. Pollack,[2] Joseph P. Boni,[4] Gary Dukart,[4] Bonnie Marshall,[4] Lisa Speicher,[4] Laurence Moore,[5] and Eric K. Rowinsky[1,2]

Abstract

Purpose: Patients with advanced cancer received temsirolimus (Torisel, CCI-779), a novel inhibitor of mammalian target of rapamycin, i.v. once daily for 5 days every 2 weeks to determine the maximum tolerated dose, toxicity profile, pharmacokinetics, and preliminary antitumor efficacy.

Experimental Design: Doses were escalated in successive cohorts of patients using a conventional phase I clinical trial design. Samples of whole blood and plasma were collected to determine the pharmacokinetics of temsirolimus and sirolimus, its principal metabolite.

Results: Sixty-three patients were treated with temsirolimus (0.75-24 mg/m^2/d). The most common drug-related toxicities were asthenia, mucositis, nausea, and cutaneous toxicity. The maximum tolerated dose was 15 mg/m^2/d for patients with extensive prior treatment because, in the 19 mg/m^2/d cohort, two patients had dose-limiting toxicities (one with grade 3 vomiting, diarrhea, and asthenia and one with elevated transaminases) and three patients required dose reductions. For minimally pretreated patients, in the 24 mg/m^2/d cohort, one patient developed a dose-limiting toxicity of grade 3 stomatitis and two patients required dose reductions, establishing 19 mg/m^2/d as the maximum acceptable dose. Immunologic studies did not show any consistent trend toward immunosuppression. Temsirolimus exposure increased with dose in a less than proportional manner. Terminal half-life was 13 to 25 hours. Sirolimus-to-temsirolimus exposure ratios were 0.6 to 1.8. A patient with non – small cell lung cancer achieved a confirmed partial response, which lasted for 12.7 months. Three patients had unconfirmed partial responses; two patients had stable disease for $\geq$24 weeks.

Conclusion: Temsirolimus was generally well tolerated on this intermittent schedule. Encouraging preliminary antitumor activity was observed.

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase and a member of the phosphatidylinositol family of kinases, which is involved in the response of eukaryotic cells to proliferative and nutritional stimuli (1–4). mTOR is downstream of Akt in the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway and regulates the ribosomal protein S6 kinase (p70 S6 kinase) and eukaryotic translation initiation factor 4E-binding protein-1. Activation of these proteins increases the translation of mRNAs with a 5′-terminal oligopyrimidine tract or 5′-cap structure, which encode for proteins involved in G_1-S cell cycle regulation (5, 6). The PI3K/Akt pathway is activated in cancer by growth factor and/or hormone receptor activation or by mutations in genes, such as *PI3K* or *PTEN*, or by *Akt* amplification (7–21).

The discovery of mTOR and the understanding of its biological functions have been greatly facilitated by studies with sirolimus (rapamycin), a naturally occurring macrolide that inhibits mTOR (2, 22). Sirolimus binds to the intracellular immunophilin FKBP12 and this complex inhibits mTOR, which results in inhibition of p70 S6 kinase and 4E-binding protein-1 functions, followed by a decrease in cyclin D1 levels, increase in p27 levels, and cell cycle arrest (23). In certain preclinical models, sirolimus induces apoptosis (24). Sirolimus also has antiangiogenesis effects by decreasing hypoxia-inducible factor-1α–induced secretion of vascular endothelial growth factor (25). Recently, sirolimus has been shown to inhibit the transforming capabilities of *PI3K* mutants (26), which supports the notion that mTOR inhibitors may be useful for the treatment of tumors with these mutations.

Temsirolimus (Torisel, CCI-779) is an ester of sirolimus (Fig. 1) selected for clinical development based on a favorable pharmacologic and toxicity profile. Temsirolimus inhibited the growth of a variety of tumor cells and was particularly effective in tumors with a defective *PTEN* gene (27–33). Temsirolimus

Authors' Affiliations: [1]Institute for Drug Development, Cancer Therapy and Research Center, Brook Army Medical Center and [2]The University of Texas Health Science Center, San Antonio, Texas; [3]Mayo Clinic, Rochester, Minnesota; [4]Wyeth Research, Collegeville, Pennsylvania; and [5]Wyeth Research, Cambridge, Massachusetts

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Requests for reprints: Manuel Hidalgo, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans Street, Room 1M89, Baltimore, MD 21231-1000. Phone: 410-502-9746; Fax: 410-614-9006; E-mail: mhidalg1@jhmi.edu.

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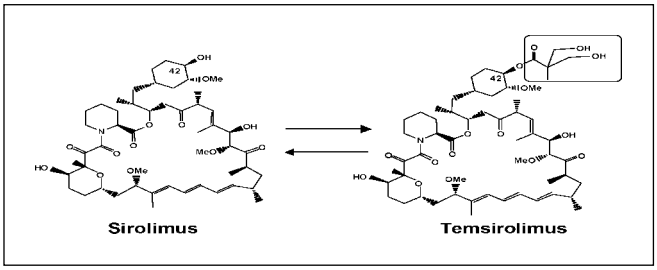

Fig. 1. Structure of temsirolimus and sirolimus, its principal metabolite.

also was effective in reversing resistance to conventional chemotherapy and hormone therapy conferred by PTEN defects (30, 34).

Because of the immunosuppressive effects of sirolimus, an expected metabolite of temsirolimus, temsirolimus was evaluated for inhibition of T lymphocyte function in euthymic mice (CCI-779 Investigator's Brochure). Although i.v. temsirolimus inhibited T lymphocyte activity, its effects were reversible and T lymphocyte activity returned to normal within 24 hours after drug treatment was stopped. Multiple cycles of temsirolimus treatment did not result in cumulative deterioration of T lymphocyte function. Further studies in mice indicated that antitumor activity could be achieved with different intermittent dosing regimens, including a daily 5-day regimen given every 2 weeks. Accordingly, this intermittent schedule was used in a phase I study to minimize the immunosuppressive effects of temsirolimus while maintaining antitumor activity.

Based on the data summarized above, temsirolimus was selected for clinical development. Three phase I single-agent studies have been conducted with this drug based on different administration regimens, including i.v. weekly (35), i.v. once daily for 5 days every 2 weeks (this study), and oral once daily for 5 days every 2 weeks (36). In this study, patients with advanced cancer were treated with temsirolimus to evaluate safety, determine the maximum tolerated dose (MTD), characterize pharmacokinetics, and seek preliminary evidence of antitumor activity.

Materials and Methods

Trial design. In this phase I, dose escalation study, temsirolimus was administered as a 30-minute i.v. infusion once daily on days 1 to 5 of each treatment cycle of ~2 weeks. Patients were observed at least 9 days after their day 5 dose of temsirolimus before receiving the next cycle of drug. Patients could remain on study as long as temsirolimus was well tolerated and there was no evidence of disease progression.

The primary objectives of the study were to determine the safety and tolerability and to identify the MTD of temsirolimus given i.v. once daily for 5 days every 2 weeks in patients with advanced solid tumors. The secondary objectives were to determine the pharmacokinetics of temsirolimus on this schedule and to obtain preliminary information on antitumor activity.

Patient selection. Patients with histologically confirmed advanced cancer (solid tumors or lymphomas) who failed to respond to standard therapy or for whom standard therapy was not available were eligible for this study. Eligibility criteria also included age ≥18 years; an Eastern Cooperative Oncology Group performance status ≤2 (ambulatory and capable of self-care); life expectancy ≥12 weeks; no prior chemotherapy, radiation therapy, or immunosuppressive therapy (except corticosteroids for management of emesis or peritumoral edema) within 3 weeks of starting study treatment; no treatment with investigational agents within 30 days before commencing study treatment; adequate hematopoietic (hemoglobin level ≥9 g/dL, absolute neutrophil count ≥1,500/μL, platelet count ≥100,000/μL), hepatic [bilirubin <1.5 mg/dL, aspartate and alanine aminotransaminases <3 times institutional normal upper limit (<5 times institutional normal upper limit for patients with liver metastases)], and renal (creatinine <2 mg/dL) functions; measurable or evaluable disease; and no active infections or history of hypersensitivity to macrolide antibiotics, unstable angina, or myocardial infarction within 6 months or coexisting medical problems of sufficient severity to limit compliance in the study. Due to the known toxicities of sirolimus, patients who entered the trial were also required to have serum levels of cholesterol and triglycerides ≤350 and ≤300 mg/dL, respectively. Patients with clinically and radiologically stable brain tumors were eligible. Patients receiving hepatic enzyme-inducing anticonvulsants or antiarrhythmic agents were ineligible. Before treatment, patients were required to give written informed consent according to federal and institutional guidelines.

Because patients who have received extensive anticancer therapy tend to have greater drug-related toxicity than those who have received less extensive therapy, patients treated with higher dose levels of temsirolimus were classified as being minimally pretreated or heavily pretreated. Heavily pretreated patients were defined as having received radiotherapy to ≥25% of bone marrow–producing areas, more than six cycles of an alkylating agent (except low-dose cisplatin), more than four courses of a carboplatin-containing regimen, or more than two courses of carmustine or mitomycin C (37).

Drug dosage and administration. The starting dose of temsirolimus was 0.75 mg/m^2 based on animal toxicology studies and prior clinical experience with sirolimus. A modified version of the Continual Reassessment Method (38, 39) was to be used to guide dose escalation.

Table 1. Patient characteristics

Characteristics	*n*
Patients	63
Fully assessable patients	60
Sex (men/women)	39/24
Age (y)	
Median	56
Range	19-79
Eastern Cooperative Oncology Group performance status, patients	
0	20
1	30
2	13
Prior therapy, patients	
Chemotherapy alone	58
Radiotherapy alone	2
Chemotherapy and radiotherapy	28
Tumor type, patients	
Renal	16
Colorectal	10
Non–small cell lung cancer	9
Soft-tissue sarcoma	7
Endometrial	3
Ovarian	2
Sarcoma	2
Other*	14

*One each of anaplastic astrocytoma, cervical, esophageal, gastric, head and neck-adenoid cystic carcinoma, hepatocellular, non-Hodgkin's lymphoma, nasopharyngeal, osteosarcoma, pancreatic, prostate, squamous cell carcinoma of the skin, thyroid, and unknown.

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Table 2. Dose escalation and toxicity experience

Temsirolimus dose (mg/m^2/d × 5)	No. patients entered (inevaluable*)	DLT (cycle 1)		No. patients reduced to dose†	Total at dose	
		No. patients	Toxicity and grade		No. evaluable patients	No. cycles
0.75	3	0		0	3	10
1.25	4 (1)	0		0	3	7
1.5	1	0		0	1	2
1.8	1	0		1	2	15
2.16	6	1	Grade 3 hypocalcemia	0	6	32
2.6	1	0		0	1	4
3.12	2	0		0	2	12
3.74	2	0		0	2	24
4.5	4	0		0	4	50
5.4	2	0		0	2	5
6.5	2	0		0	2	10
7.8	3	0		0	3	29
9.4	1	0		0	1	3
11.3	4 (1)	0		1	4	17
Minimally pretreated						
15	3	1	Grade 3 hyperglycemia	2	5	33
19	6	0		3	9	45
24	6	1	Grade 3 stomatitis	0	6	24
Heavily pretreated						
15	6 (1)	0		5‡	10	31
19	6	2	Grade 3 aspartate and alanine aminotransaminase elevations Grade 3 vomiting, diarrhea, and asthenia	0	6	7
Total	63 (3)	4				361

*Reasons inevaluable for determining dose escalation: two disease progression (1.25 and 15 mg/m^2/d) during cycle 1 and one hypersensitivity reaction (11.3 mg/m^2/d) during the first 24 hours after the first temsirolimus dose.
†Includes all patients reduced from the next higher dose level at any subsequent cycle.
‡One patient required a second dose reduction to 11.3 mg/m^2/d.

However, because of adverse events observed at the first two dose levels and after discussions with the U.S. Food and Drug Administration, the protocol was amended and a fixed 20% dose escalation was used. A later amendment allowed fixed dose escalation increments of up to 30%.

The National Cancer Institute Common Toxicity Criteria version 2.0 was used to grade toxicity. Unacceptable toxicities included temsirolimus-related (*a*) grade 3/4 nonhematologic toxicity (excluding nausea or vomiting in patients on suboptimal antiemetic prophylaxis or serum triglycerides <1,500 mg/dL if recovery occurred by the next cycle), (*b*) grade 4 thrombocytopenia, or (*c*) grade 4 neutropenia lasting >5 days. If a patient had an unacceptable toxicity, dose reduction by one to two levels and/or a delay in treatment could occur. If a grade 3 toxicity was observed in a patient at a given dose level, the cohort was

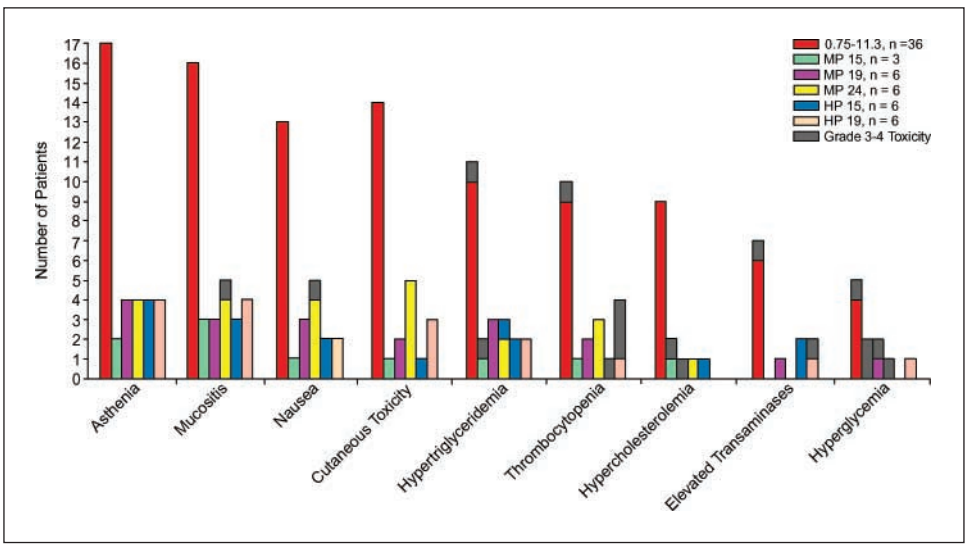

Fig. 2. Frequently occurring toxicities of temsirolimus included, for all 63 patients, asthenia (35 patients, 56%), mucositis (34 patients, 54%), nausea (26 patients, 41%), cutaneous toxicity (26 patients, 41%), hypertriglyceridemia (23 patients, 37%), thrombocytopenia (21 patients, 33%), hypercholesterolemia (14 patients, 22%), elevated transaminases (12 patients, 19%), and hyperglycemia (11 patients, 17%). Temsirolimus doses: 0.75 to 11.3, 15, 19, and 24 mg/m^2/d. MP, minimally pretreated; HP, heavily pretreated.

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Table 3. Pharmacokinetic variables of temsirolimus on day 5, mean ± SD (no. patients)

Dose group (mg/m^2)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (cycle 1; ng h/mL)
0.75	72 ± 16 (3)	0.67 ± 0.29 (3)	24.8 ± 7.5 (2)	1,355 ± 732 (2)
1.25	133 ± 64 (3)	0.46 ± 0.28 (30)	12.6 ± 5.1 (3)	2,502 ± 1,531 (3)
2.16	186 ± 51 (5)	0.59 ± 0.24 (5)	16.4 ± 6.9 (5)	3,896 ± 986 (5)
4.5	331 ± 72 (4)	0.46 ± 0.11 (4)	13.9 ± 2.6 (4)	5,350 ± 792 (4)
15	503 ± 293 (5)	0.26 ± 0.18 (5)	20.0 ± 22.0 (5)	8,619 ± 2,188 (5)
19	796 ± 226 (12)	0.41 ± 0.13 (12)	15.4 ± 15.6 (12)	9,838 ± 3,504 (12)

Abbreviations: C_{max}, peak observed concentration; t_{max}, time to C_{max}; $t_{1/2}$, terminal half-life; AUC, area under the concentration versus time curve; CL_c, central clearance; Vd_{ss}, steady-state volume of distribution; AR, accumulation ratio of day 5 to day 1; B/P_{ratio}, blood-to-plasma concentration ratio.

expanded to three patients. If an unacceptable toxicity was observed in a patient at a given dose level in cycle 1, a dose-limiting toxicity (DLT) occurred and that cohort was expanded to six patients. The MTD was defined as the highest dose for which two or fewer patients had a DLT. However, the combination of DLTs and dose reductions that occurred at a given dose level were taken into account in identifying the MTD.

Temsirolimus (25 mg/mL in 100% ethanol, Wyeth Research, Collegeville, PA) is a light-sensitive drug and was protected from sunlight and unshielded fluorescent light during preparation and administration. The drug-ethanolic concentrate was diluted 10-fold in a polyethylene glycol/polysorbate diluent and then further diluted with 0.9% saline solution to a total volume of 50 to 100 mL, which was administered for ~30 minutes using glass or polyolefin infusion kits and an automatic dispensing pump.

Evaluation of patients. Physical examination and routine laboratory evaluations were done before treatment and weekly.

For assessment of immunologic activity, whole blood samples were collected before treatment, on days 1 and 5 of cycles 1 to 3, and on day 8 of cycle 1. Three assays were done. (*a*) WBC counts and differentials were monitored to check for changes in lymphocyte numbers. (*b*) Proliferative responses (uptake of tritiated thymidine) of patient's lymphocytes to pokeweed mitogen, phytohemagglutinin, and concanavalin A and to pooled allogeneic cells were monitored as standard indicators of altered lymphocyte function (40). (*c*) Lymphocyte subsets (cell surface phenotypes CD4/CD3, CD8/CD3, CD14, and CD45 and the CD4/CD3:CD8/CD3 ratio) were monitored using standard methods (41). Measured variables were graphically depicted and visually analyzed.

Radiologic studies for disease assessment were repeated after alternate cycles or as needed. A complete response was reported if there was disappearance of all active disease. A partial response was reported if there was at least a 50% reduction in total tumor size (the sum of the product of the bidimensional measurements of all lesions). A confirmed response was reported if two measurements separated by a minimum of 4 weeks indicated a response and an unconfirmed response was reported if a response occurred but did not meet the criteria required for a confirmed response. Stable disease was scored if there was <50% reduction in total tumor size or <25% increase in the size of one or more measurable lesions. An increase in the size of one or more measurable lesions by at least 25% or the appearance of any new lesion was considered disease progression (42). Clinical benefit included the number of patients with confirmed and unconfirmed complete and partial responses and the number of patients with stable disease for at least 24 weeks. Time to tumor progression was measured from day 1 of temsirolimus treatment until documented disease progression.

Pharmacokinetic analyses. Whole blood samples for the determination of temsirolimus and sirolimus concentrations were collected in sodium EDTA tubes (3 mL each) in cycles 1 and 3: on days 1 and 5 at 0 (before treatment), 0.25, 0.50, 1, 2, 4, and 6 hours; on days 2 to 4 at 0 hours; and on days 8, 10, and 12. The samples were frozen at −70°C until assayed. To determine the blood to plasma partitioning of temsirolimus, 6 mL blood samples were collected in cycle 1 on days 1 and 5 at 0.5 hour after drug administration and in cycle 2 on day 1 before drug administration. These samples were centrifuged immediately and the plasma was stored at −70°C until assayed.

Temsirolimus and sirolimus concentrations in whole blood were measured using a liquid chromatography-tandem mass spectrometry procedure (Taylor Technology, Inc., Princeton, NJ) as described (35). Both temsirolimus and sirolimus concentration data were analyzed by noncompartmental methods. A compartmental model was also used to fit temsirolimus concentration data. Pharmacokinetic analyses were based on concentrations derived in whole blood due to the limited stability of temsirolimus in plasma. A two-compartment open model was fit to the concentration data with dose administration and elimination from the central compartment. Variable estimation for each patient and treatment period was individually derived using the maximum likelihood estimation algorithm in the ADAPTII software, release 4, March 1997 (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA).

Dose-dependent variables were normalized and all pharmacokinetic variables were log transformed before performing ANOVA. The ANOVA assessed variability factors for course (j) and patient (k) using the model: $y_{jk} = \mu + \text{course}_j + \text{patient}_k + \varepsilon_{jk}$, in which μ is the overall mean and ε is the within-patient random error in variable y. Statistical

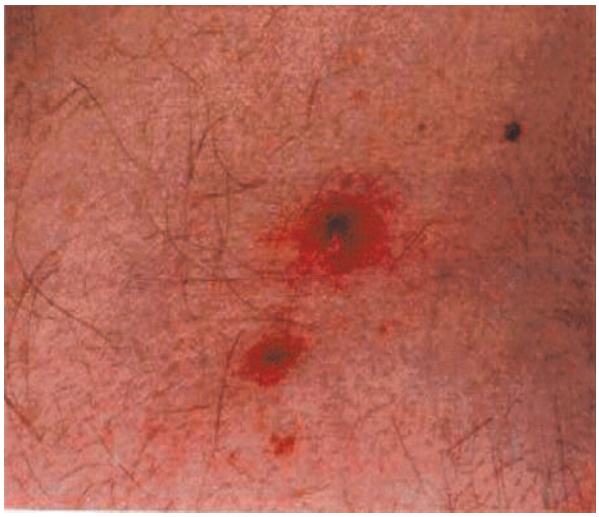

Fig. 3. Representative pustular skin rash in a patient treated with temsirolimus.

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Table 3. Pharmacokinetic variables of temsirolimus on day 5, mean ± SD (no. patients) (Cont'd)

AUC (cycle 3; ng h/mL)	CL_c (L/h)	Vd_{ss} (L)	AR	B/P_{ratio} (day 1)
—	6.2 ± 3.3 (2)	132.1 ± 14.2 (2)	2.2 ± 1.1 (3)	10.9 ± 13.9 (2)
2,812 (1)	5.2 ± 2.7 (3)	57.1 ± 21.7 (3)	1.0 ± 0.6 (3)	10.4 ± 3.2 (4)
4,705 ± 1,781 (3)	5.5 ± 1.4 (5)	81.5 ± 23.7 (5)	1.3 ± 0.4 (5)	9.1 ± 6.3 (6)
5,439 ± 2,223 (3)	7.6 ± 1.5 (4)	111.1 ± 8.7 (4)	1.1 ± 0.2 (4)	3.7 ± 1.7 (4)
7,756 (1)	16.5 ± 5.3 (5)	232.5 ± 110.9 (5)	0.7 ± 0.4 (4)	1.5 ± 0.9 (6)
9,353 ± 1,053 (4)	19.9 ± 7.5 (12)	239.2 ± 116.0 (12)	0.8 ± 0.1 (11)	1.5 ± 0.6 (12)

differences with $P < 0.05$ were considered significant. Before statistical analysis, C_{max} was normalized to the daily temsirolimus dose, and AUC and AUC_{sum} were normalized to the cumulative dose administered over the respective 2-week cycle. All available data were included in the statistical analysis. To assess the proportionality of exposure with dose, C_{max}, AUC, and AUC_{sum} were analyzed using the power model $Y = \alpha DOSE^{\beta}$, in which Y is the pharmacokinetic variable of interest, β is the variable estimate for slope, and α is the intercept. For this analysis, the null hypothesis, H_o: $\beta = 1$ was tested. Rejection of H_o indicates that the relationship between Y and DOSE is not proportional.

Results

General. A total of 63 patients, whose relevant characteristics are shown in Table 1, were enrolled on this study from August 1998 to May 2000. The last patient completed the study in February 2002. Patients received a total of 361 2-week cycles of temsirolimus. The median number of cycles administered per patient was 4 (range, 1-21). Fifty-eight patients had received prior treatment with chemotherapy alone and 30 had received prior treatment with radiation therapy either alone (2) or combined with chemotherapy (28).

Dose escalation. The results of the temsirolimus dose escalation are shown in Table 2. The first patient in the 0.75 mg/m^2/d cohort experienced grade 3 neutropenia. Because of this grade 3 toxicity, the cohort was expanded to three patients as dictated by the protocol. The two additional patients who were treated at this dose developed no adverse events. The first patient in the next cohort (1.25 mg/m^2/d) also experienced grade 3 neutropenia and three additional patients were treated at this dose and developed no adverse events. No DLTs were observed until the 2.16 mg/m^2/d cohort. In this cohort, one patient had a DLT of grade 3 hypocalcemia; five additional patients were treated and had no DLTs. Dose escalation continued without additional DLTs until the 15 mg/m^2/d cohort. In this cohort, one patient had a DLT of grade 3 hyperglycemia; two additional patients were treated and had no DLTs. In the 19 mg/m^2/d cohort, one patient had DLTs of grade 3 elevations in transaminases; five additional patients were treated and one of these had grade 3 thrombocytopenia. To further evaluate this dose level, six additional patients were treated and one patient had DLTs of grade 3 vomiting, diarrhea, and asthenia and two had grade 3 thrombocytopenia, which required dose reductions. The two patients with the DLTs and the three with the dose reductions in the 19 mg/m^2/d cohort were heavily pretreated. Thus, the decision was made to classify patients based on whether they had been heavily pretreated or minimally pretreated for the remainder of the dose escalation.

Five additional heavily pretreated patients were treated with 15 mg/m^2/d temsirolimus for a total of six in the heavily pretreated cohort and no DLTs were observed. Of the six heavily pretreated patients who had been treated with 19 mg/m^2/d temsirolimus, two had DLTs and three required dose reductions. Based only on DLTs, the MTD would have been 19 mg/m^2/d but, because of the dose reductions, the dose of 15 mg/m^2/d was considered the MTD for heavily pretreated patients.

Six minimally pretreated patients had been treated with 19 mg/m^2/d temsirolimus and none had DLTs. Thus, six minimally pretreated patients were treated with 24 mg/m^2/d temsirolimus. One had a DLT of grade 3 stomatitis and two required dose reductions, one because of grade 2 thrombocytopenia and the other because of grade 2 erythema nodosum. Based on the DLT and the two dose reductions, a MTD was not formally identified but the dose of 19 mg/m^2/d was considered the maximum acceptable dose in minimally pretreated patients.

Toxicity. Selected temsirolimus-related toxicities as a function of dose that occurred in at least 10% of patients in any treatment cycle are summarized in Fig. 2. The most common drug-related adverse events observed across all dose levels were asthenia (56%), mucositis (54%), nausea (41%), and cutaneous toxicity (41%). The two most frequent drug-related grades 3 to 4 adverse events were hypophosphatemia and hyperglycemia in 11% and 8% of patients, respectively. Overall, 10 patients required dose reductions; 7 of these and 20 additional patients required dose delays.

Hematologic toxicity consisted mainly of thrombocytopenia (33%) and leukopenia (27%). Grade 3 thrombocytopenia occurred in five patients, including three heavily pretreated patients treated at the 19 mg/m^2/d dose (Fig. 2). Thus, this incidence seemed to be dose related. Thrombocytopenia was the most common cause for dose reductions and delays (four patients with both and seven with only delays). Five patients developed grade 3 neutropenia; three were treated with <15 mg/m^2/d temsirolimus, suggesting that severe neutropenia was not dose related. Neutropenia contributed to dose reduction and delay in one patient. Seventeen (27%) patients developed temsirolimus-related grades 1 to 2 epistaxis, which resolved rapidly; 10 were treated with doses of at least 15 mg/m^2/d.

Treatment with temsirolimus resulted in few severe nonhematologic toxicities. Although 54% of patients developed mucositis, only one patient who was treated with 24 mg/m^2/d temsirolimus developed grade 3 mucositis, a DLT (Table 2). Drug-related cutaneous toxicity was commonly observed in patients treated with temsirolimus over a wide range of doses

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Table 4. Pharmacokinetic variables of sirolimus on day 5, mean ± SD (no. patients)

Dose group (mg/m^2)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (cycle 1; ng h/mL)
0.75	9.3 ± 4.1 (3)	25.9* ± 37.5 (3)	102.0 ± 46.3 (3)	1,866 ± 1,324 (3)
1.25	27.3 ± 7.6 (3)	3.6 ± 2.2 (3)	80.3 ± 15.5 (3)	4,186 ± 1,293 (3)
2.16	34.3 ± 21.2 (5)	3.6 ± 2.1 (5)	49.4 ± 27.2 (6)	3,240 ± 2,463 (6)
4.5	48.7 ± 16.7 (4)	2.8 ± 2.3 (4)	50.3 ± 6.8 (4)	5,583 ± 2,728 (4)
15.0	57.8 ± 24.3 (5)	1.8 ± 1.5 (5)	39.9 ± 1.3 (2)	4,729 ± 545 (2)
19.1	133.9 ± 70.3 (12)	2.0 ± 1.5 (12)	52.3 ± 14.5 (11)	15,503 ± 8,573 (11)

Abbreviations: AUC_{ratio}, uncorrected ratio of sirolimus to temsirolimus AUC; AUC_{sum}, arithmetic sum of temsirolimus and sirolimus AUC.
*One of three patients exhibited an abnormally prolonged t_{max}.

(26 total patients, 41%; Fig. 2). These included maculopapular rashes, acne, pustular rashes (Fig. 3), and pruritus. All skin reactions were grades 1 to 2 in severity and reversible. One patient treated with 24 mg/m^2/d temsirolimus presented on day 94 with a clinical picture consistent with erythema nodosum (grade 2), which was considered to be possibly related to study medication, resulted in a dose reduction, and resolved with prednisone treatment. Three patients developed symptoms consistent with an allergic drug reaction, which began shortly after the start of the first i.v. infusion and ended after stopping the infusion. One patient treated with 11.3 mg/m^2/d temsirolimus developed a grade 4 allergic reaction and discontinued treatment. The other two patients were treated with 24 mg/m^2/d temsirolimus, developed grades 1 and 3 allergic reactions, and had dose delays.

Some laboratory abnormalities were frequently reported as adverse events. Temsirolimus-related hyperglycemia was reported in 11 (17%) patients and was grades 3 to 4 in 5 (8%) patients (Fig. 2). Hyperglycemia was a DLT for one patient treated with the 15 mg/m^2/d dose (Table 2). Temsirolimus-related elevations in plasma triglyceride and cholesterol levels occurred in 23 (37%) and 14 (22%) patients, respectively, and reached grades 3 to 4 levels in 3 (5%) and 2 (3%) patients, respectively (Fig. 2). One minimally pretreated patient treated with the 15 mg/m^2/d dose developed grade 3 hypertriglyceridemia and discontinued treatment. Other temsirolimus-related grades 3 to 4 laboratory abnormalities included hypophosphatemia (7 patients, 11%), hypokalemia (3 patients, 5%), and hypocalcemia (2 patients, 3%). Hypocalcemia was a DLT for one patient treated with the 2.16 mg/m^2/d dose. Elevations of aspartate and alanine aminotransaminases occurred in 9 (14%) and 8 (13%) patients, respectively. Elevations in aspartate and alanine aminotransaminases were DLTs in one heavily pretreated patient treated with the 19 mg/m^2/d dose.

Immunologic studies. There were no episodes of infections or any other clinical manifestation that indicated an opportunistic infection or immunosuppressed state. Lymphocyte cell surface phenotype analysis and mitogen proliferation assays did not show any consistent trend toward immunosuppression (data not shown). Although intersubject variability was considerable, results for individual patients were consistent. Proliferative responses to mitogens and pooled allogeneic cells were within the control ranges, with two exceptions that recovered to the reference range within the study period.

Pharmacokinetic analysis. Whole blood and plasma samples were available from 62 patients receiving doses of 0.75 to 24 mg/m^2 (1.42-55.2 mg). Following drug administration, temsirolimus concentrations decreased with time in a polyexponential manner. A summary of relevant pharmacokinetic variables measured for temsirolimus and sirolimus is provided in Tables 3 and 4, respectively. Figures 4 and 5 show the relationship between temsirolimus exposure (C_{max} and AUC, respectively) and dose. Over the wide range of doses evaluated, temsirolimus exposure increased with dose in a less than proportional manner. Steady-state volume of distribution (Vd_{ss}) was extensive, increased with dose, and exhibited values typically exceeding total body weight. At <15 mg/m^2, temsirolimus exhibited preferential partitioning into RBC, with mean blood-to-plasma ratios of 3.7 to 10.9 (coefficient of variation, 31-128%), whereas at ≥15 mg/m^2 the ratios approached unity. Mean clearance from whole blood increased with increasing dose from 5.2 to 19.9 L/h and was associated with modest to moderate intersubject variability (coefficient of variation, 20-54%). Mean terminal half-life was 13 to 25 hours.

Sirolimus was a major metabolite that was observed early (after 15 minutes of infusion) and decreased with time in an apparent monoexponential or biexponential fashion. Sirolimus exposure was generally comparable with temsirolimus exposure, with sirolimus-to-temsirolimus AUC ratios of 0.6 to 1.8. No statistically significant differences in pharmacokinetic variables were apparent when cycle was a factor in ANOVA analysis, a finding consistent with limited degrees of drug accumulation observed with multiple cycles of treatment. No age-related (Figs. 4 and 5) or sex-related effects were apparent.

Analysis of toxicity events as a function of exposure revealed a positive correlation between temsirolimus C_{max} and the severity of thrombocytopenia (P = 0.014). Temsirolimus AUC showed a positive correlation with the severity grades of aspartate aminotransaminase elevation and hypocalcemia (P = 0.012 and 0.030, respectively). Sirolimus AUC showed a positive correlation with the severity grades of hypophosphatemia and thrombocytopenia (P = 0.003 and 0.011, respectively). AUC_{sum} were positively related with the severity grades of hypertriglyceridemia and hyperglycemia (P = 0.033 and 0.041, respectively).

Antitumor effects. A 68-year-old man with non–small cell lung cancer who received 7.8 mg/m^2/d temsirolimus had a confirmed partial response, which was reported 1.4 months after the first dose and lasted for 12.7 months. Three patients had unconfirmed partial responses lasting ~1 to 5 months. These included a patient with renal cancer who received 3.7 mg/m^2/d temsirolimus, another patient with renal cancer who received 19 mg/m^2/d temsirolimus for 5 cycles and then

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Table 4. Pharmacokinetic variables of sirolimus on day 5, mean ± SD (no. patients) (Cont'd)

AUC (cycle 3; ng h/mL)	AR	AUC_{ratio}	AUC_{sum} (ng h/mL)
1,929 ± 1,132 (2)	1.8 ± 0.5 (2)	1.2 ± 0.8 (2)	3,194 ± 2,603 (2)
3,688 (1)	1.3 (1)	1.7 ± 1.5 (2)	7,144 ± 182 (2)
5,309 ± 90 (3)	1.2 ± 0.4 (3)	0.9 ± 0.4 (5)	7,740 ± 2,977 (5)
4,815 ± 1,488 (3)	1.1 ± 0.3 (3)	1.0 ± 0.4 (4)	10,934 ± 3,384 (4)
2,958 (1)	—	0.6 ± 0.2 (2)	12,687 ± 4,050 (2)
11,857 ± 4,724 (4)	0.5 ± 0.3 (3)	1.8 ± 1.2 (11)	2,4781 ± 8,956 (11)

15 mg/m^2/d, and a patient with soft-tissue sarcoma who received 2.16 mg/m^2/d temsirolimus. Two patients had stable disease for at least 24 weeks, one with nasopharyngeal cancer who received 4.5 mg/m^2/d temsirolimus and one with gastric cancer who received 24 mg/m^2/d for 5 cycles and then 19 mg/m^2/d. Thus, six patients had suggestive evidence of clinical benefit.

The median time to tumor progression for all patients was 2.9 months (95% confidence interval, 1.9-4.2 months). No relationships between time to tumor progression and indices reflecting drug exposure were evident.

Discussion

This study explored the toxicity, pharmacology, and preliminary antitumor activity of the novel mTOR inhibitor temsirolimus administered daily for 5 days every 2 weeks in patients with advanced cancer. Heavily pretreated patients did not tolerate doses of temsirolimus above 15 mg/m^2/d. Therefore, this dose was established as the MTD. Minimally pretreated patients tolerated doses up to 24 mg/m^2/d without reaching a formal MTD. However, frequent dose reductions and treatment delays indicated that the 19 mg/m^2/d dose was the maximum acceptable dose. Temsirolimus exposure increased less than proportionally with dose. The terminal half-life was 13 to 25 hours. Sirolimus was a principal metabolite. A patient with non–small cell lung cancer achieved a durable confirmed partial response and six total patients with various tumor types had clinical benefit. Based on these results and data from a parallel phase I study that explored a weekly schedule of temsirolimus (35), this drug is being developed in disease-oriented studies. Subsequent phase II studies using the weekly schedule support the notion that temsirolimus has activity in patients with renal and breast cancer, glioblastoma multiforme, and mantle cell lymphoma (43–46).

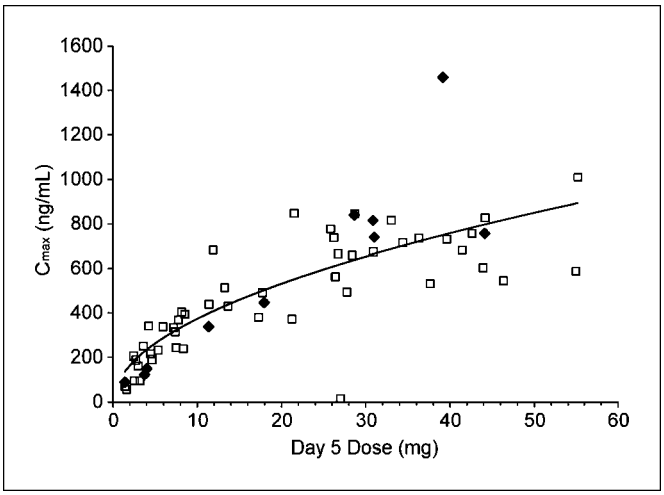

Fig. 4. Temsirolimus C_{max} in whole blood versus the day 5 dose during cycle 1. □, patients age <65 years; ♦, age ≥65 years.

Temsirolimus was generally well tolerated in this intermittent schedule of administration and resulted in expected manageable toxicities of mild to moderate intensity. The most frequently occurring temsirolimus-related adverse events were asthenia, mucositis, nausea, and cutaneous toxicity. Three patients also developed symptoms of an allergic drug reaction during infusion of temsirolimus. Therefore, in subsequent studies, patients have been pretreated with diphenhydramine before the temsirolimus infusion (43, 44). Detailed immunologic studies, including lymphocyte number, subset analysis, and response to mitogens, suggested that temsirolimus treatment had no consistent effect on lymphocyte populations and activation. Furthermore, the clinical toxicities observed did not suggest that immunosuppression was a concern. Although a subsequent study with temsirolimus reported cases of possible pneumonitis, these were nonspecific and not associated with an infectious process (43). The toxicity spectrum of temsirolimus on this administration schedule was similar to that observed when the drug was given weekly, although the incidence of mucositis and skin reactions was more pronounced in the weekly administration regimen (35). The toxicities of this agent were not substantially different from those that have been observed in clinical trials with other mTOR inhibitors, such as everolimus, AP23573, and sirolimus itself (47, 48). Thus, these toxicities likely result from a common target-based etiology (i.e., mTOR inhibition) and not immunosuppression or idiopathic phenomena because AP23573 and everolimus are not metabolized to sirolimus in humans (49, 50).

An interesting observation in this study, which is also supported by data from other temsirolimus studies, is the lack of clear dose relatedness in the frequency and severity of many of the toxicities (35, 43, 44). The less than proportional increase in exposure with dose and the substantial interpatient variability in temsirolimus whole blood concentrations may explain, in part, why most toxicities were not dose related. These results illustrate the limitations of toxicity-only-driven clinical trials to determine the phase II dose for molecularly targeted drugs with low toxicity. It is becoming increasingly clear that factors in addition to toxicity and pharmacokinetics need to be considered in this process. Recently, the focus of attention has been to determine the pharmacodynamic effects of an agent using either biological tests or imaging methods. With regard to mTOR inhibitors, studies have focused on measuring p70 S6 kinase activity in normal and surrogate

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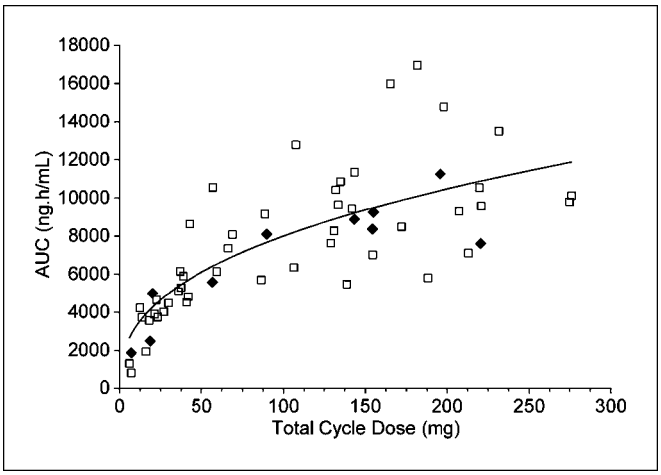

Fig. 5. Temsirolimus AUC in whole blood versus total dose during cycle 1. □, patients age <65 years; ♦, age ≥65 years.

tissues as a determinant of drug activity (51, 52). This analysis has been incorporated into the phase I development of newer mTOR inhibitors, such as everolimus and AP28574 (49, 50, 53). However, until a marker has been validated, it is appropriate to explore a full dose range in phase I studies.

An intense area of investigation for mTOR inhibitors is the identification of factors that may predict the susceptibility of a tumor. At least three complementary lines of evidence suggest that a tumor with hyperactivation of the PI3K/Akt signaling pathway is particularly susceptible to these drugs. First, *in vitro* and *in vivo* studies using a variety of cancer models showed that tumors with defective PTEN have a heightened response to mTOR inhibition (29, 32, 33, 54). Second, in other studies, mTOR inhibition blocked the tumorigenic effects of genetically activated Akt in prostate cancer models (55). Third, in a recent phase II trial of weekly temsirolimus in patients with recurrent glioblastoma multiforme, elevated baseline tumor phosphorylated p70 S6 kinase levels, as assessed by immunohistochemistry, were associated with neuroimaging response (45). Additional clinical data will be necessary to determine whether phosphorylated p70 S6 kinase or other components of the PI3K/Akt signaling pathways predict the outcome of patients treated with mTOR inhibitors. Such analysis may offer the opportunity for a more rational disease-oriented evaluation.

In summary, the results of this study indicate that temsirolimus is generally well tolerated when administered daily for 5 days every 2 weeks in cancer patients. Preliminary evidence of antitumor activity was noted in several advanced solid malignancies. Future studies should aim to further evaluate antitumor activity and safety and to identify the pharmacodynamic effective dose of temsirolimus and biological factors that may be predictive of a positive outcome in cancer patients.

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Manuel Hidalgo, Jan C. Buckner, Charles Erlichman, et al.

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