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ORIGINAL ARTICLE

A phase I study of daily everolimus plus low-dose weekly cisplatin for patients with advanced solid tumors

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Abstract
Purpose Preclinical studies demonstrate synergistic anti-tumor activity with the combination of everolimus and cisplatin. We conducted a phase I study to establish the recommended phase II of oral everolimus to be given with low-dose weekly intravenous cisplatin.
Methods Part A used a standard 3 + 3 dose escalation scheme. There were 4 planned dose levels of everolimus: 2.5, 5, 7.5, and 10 mg/day. Subjects received oral everolimus during days 1–21 and cisplatin 20 mg/m^2 intravenously (fixed dose) on days 1, 8, and 15 of a 28-day cycle. Pharmacokinetic (PK) blood samples were collected on day 1 and day 8 of cycle 1 in Part A. After the phase II recommended dose was established (Part A), 6 additional subjects were enrolled in an expansion cohort (Part B). Response was assessed by RECIST q 2 cycles for all subjects.
Results Thirty patients were enrolled (18 male, 12 female) and 29 were treated. Median age was 61 years (31–79) and the median number of prior cytotoxic chemotherapy regimens was 2 (0–3). Eighty-three percent of subjects had received prior RT. DLTs occurred at dose level 1 (sudden death of unclear cause in a patient with melanoma metastatic to liver) and dose level 2 (bowel obstruction). No DLTs occurred at dose levels 3 and 4. The most common adverse events (≥grade 3) among 28 patients evaluable for toxicity were lymphopenia (36%), hyperglycemia (11%), fatigue (11%), and venous thrombosis (11%). PK analysis of everolimus demonstrated dose-proportional increases in C_{max} (mean 91.9 ng/ml) and $AUC_{0\text{-}INF}$ (mean 680.5 h*ng/ml) at dose level 4. Three partial responses were seen (metastatic pulmonary carcinoid, $n = 2$; metastatic sinus carcinoma, $n = 1$). Prolonged stable disease ≥6 cycles occurred in subjects with pulmonary carcinoid, oropharyngeal squamous cell carcinoma, basal cell carcinoma, papillary thyroid carcinoma, and esthesioneuroblastoma ($n = 1$ each).
Conclusion The phase II recommended dose is everolimus 10 mg/day (days 1–21) + cisplatin 20 mg/m^2 (days 1, 8, and 15) of a 28-day cycle. PK data demonstrate dose-proportional increases in exposure, as previously described for everolimus monotherapy. Anti-tumor activity was observed in several tumor types.

Keywords Everolimus · Cisplatin · Phase I · Solid tumor

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Introduction

Cisplatin (*cis*-diamminedichloroplatinum, CDDP) is a platinum coordination complex that is typically administered intravenously at high dose (≥75 mg/m^2) every 3 weeks and has significant anti-tumor activity against a wide range of solid tumor types [1]. Toxicities can include nephrotoxicity, bone marrow suppression, peripheral neuropathy,

ototoxicity, emesis, and fatigue [1]. Low-dose cisplatin (20–30 mg/m^2 per week) may be less toxic, and regimens of low-dose cisplatin plus other cytotoxic drugs have been evaluated in phase I and phase II studies [2–10]. Development of these doublet regimens may be limited by toxicities associated with the second cytotoxic agent, and weekly low-dose cisplatin doublet regimens generally have not supplanted the traditional high-dose cisplatin regimens as systemic therapy for any solid tumor type. New doublets are needed in which low-dose cisplatin synergizes with novel agents targeting cancer cell-specific survival pathways, potentially improving anti-tumor efficacy while resulting in less toxic effect on normal tissue.

Aberrant signaling in the PI3K/Akt/mTOR (phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin) pathway drives the malignant phenotype of many solid tumors [11]. Activation of the pathway may be due to somatic mutation in the gene encoding the catalytic subunit of PI3K (*PIK3CA*), activation of receptor tyrosine kinases upstream of PI3K, loss or inactivation of the PTEN suppressor gene, or genetic lesions in Akt or other downstream signaling molecules [11–13]. A major downstream effector in this pathway is mTOR, a serine/threonine kinase that resides in two multiprotein complexes (mTORC1 and mTORC2) that regulate transcription, protein translation, metabolism, cell growth, and survival [14]. Two well-characterized phosphorylation targets of mTORC1 are eIF4E-binding protein (4E-BP1) and the 70 kD ribosome S6 protein kinase (S6K1), which regulate translation of proteins required for G1-S phase progression in the cell cycle.

Everolimus (RAD001, Afinitor®), an orally available macrolide derivative of rapamycin, binds the intracellular 12-kilodalton immunophilin FK506-binding protein (FKBP12) with high affinity. The resulting FKBP12/RAD001 complex then inhibits mTORC1 activity. Everolimus monotherapy (10 mg/daily) has received FDA approval as palliative therapy for patients with advanced renal carcinoma. A phase III trial randomized 410 patients with metastatic renal cell carcinoma (after progression on VEGF receptor tyrosine kinase inhibitor therapy) to everolimus or placebo. On the experimental arm, there was improved progression-free survival when compared with placebo (4.0 months vs. 1.9 months, $P < 0.0001$) [15]. The most common grade 3–4 adverse events were anemia (7% for RAD001 vs. 5% for placebo) and stomatitis (4% vs. 0%). Ten percent of patients had adverse events leading to discontinuation with RAD001, versus 4% with placebo. Everolimus therapy also has demonstrated anti-tumor activity for patients with advanced gastrointestinal neuroendocrine tumors [16, 17].

Inhibition of mTOR may provide a strategy to sensitize cancer cells to conventional cytotoxic chemotherapy. In 1995, Mills et al. reported rapamycin enhances the cytotoxic effects of cisplatin against a human leukemia cell line (HL-60) and an ovarian cancer cell line (SKOV3) [18]. The fundamental observation that mTOR inhibitors sensitize tumor cells to platinum chemotherapy has been confirmed by several groups [19–22]. The mechanism underlying the synergistic activity between mTOR inhibitors and cisplatin against certain cell lines has not been conclusively established, but it has been proposed that everolimus sensitizes cancer cells to cisplatin by reducing cellular levels of p21, thereby impairing DNA repair in cancer cells treated with low-dose cisplatin and resulting in cell death [19].

In summary, preclinical data have shown consistently that mTOR inhibition enhances the activity of cisplatin against solid tumor cell lines, potentially facilitating the clinical development of low-dose cisplatin regimens with reduced toxicity. Therefore, we conducted a phase I study to determine the phase II recommended dose of daily oral everolimus administered with weekly intravenous low-dose cisplatin (20 mg/m^2) on a 3 weeks on, 1 week off schedule.

Patients and methods

Patient eligibility

This was an open label, single institution trial approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center (MSKCC). All subjects provided written informed consent. The study was open to adult subjects ($\geq$18 years of age) with advanced solid tumors not curable by surgery or radiation therapy. Pathologic confirmation at MSKCC of the diagnosis of advanced solid tumor was required.

Subjects were required to have Karnofsky Performance Status $\geq$70%. Subjects must not have received more than 3 prior cytotoxic chemotherapy regimens in the recurrent or metastatic disease setting, or prior radiation therapy to >25% of bone marrow. Required laboratory parameters were as follows: absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, hemoglobin >10 g/dL, serum bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), serum transaminases (alanine aminotransferase, ALT; aspartate aminotransferase, AST) activity $\leq 1.5 \times$ ULN, serum creatinine within institutional normal limits, or calculated creatinine clearance (by Cockcroft and Gault method) $\geq$55 ml/min for patients with creatinine limits above institutional normal. For women of child-bearing potential, a negative urine or serum pregnancy test was required within 14 days prior to administration of everolimus.

Exclusion criteria included the following: prior treatment with everolimus or other mTOR inhibitor, other active malignancy (other than indolent malignancies which the investigator determines are unlikely to interfere with treatment

and safety analysis), peripheral neuropathy ≥grade 3, hypertriglyceridemia ≥grade 2, uncontrolled brain or leptomeningeal metastases, impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus, radiotherapy within 4 weeks or major surgery within 2 weeks prior to study enrollment, or any active infection or serious underlying medical condition that would impair the patient's ability to receive protocol treatment. HIV-positive patients were excluded; pharmacokinetic interactions between antiretroviral therapy and the study regimen may be problematic for these patients. Patients who require chronic treatment with steroids (>prednisone 5 mg/day) or other immunosuppressive agents were excluded.

Dose-limiting toxicity (DLT)

Toxicity was assessed using NCI Common Toxicity Criteria (CTC) version 3.0. DLT was defined as febrile neutropenia, grade 4 neutropenia for ≥7 days, other grade 4 hematologic toxicity, or any other nonhematologic grade 3 or 4 treatment-related toxicities, excluding nausea, vomiting, rash, untreated hyperlipidemia, grade 3 diarrhea lasting <48 h, or grade 3 fatigue lasting ≤7 days. Any toxicity requiring treatment delay for >7 days was considered DLT. The period of DLT-monitoring was cycle 1 only (28 days).

Dose escalation and definition of maximum-tolerated dose (MTD)

The starting dose of everolimus was 2.5 mg/day. The dose escalation plan for everolimus is shown in Table 1. The study followed a standard 3 + 3 dose escalation design. Completion of one cycle of therapy (28 days) by all subjects at any dose level was required before any subjects could be enrolled at the next dose level. Three subjects were enrolled at the first dose level; if no DLT was observed, three subjects were enrolled at the next dose level. If one DLT was observed, the dose level was expanded to six subjects. If none of these additional three patients experienced DLT, escalation to the next higher dose level was allowed. If at least one of the additional patients experienced DLT, the MTD would be exceeded and the next lowest dose level would be expanded to a total of 6 subjects. This lower dose would then become the phase II recommended dose if no more than 1 patient experienced a DLT. If ≤1 of the first 3 patients experienced DLT at dose level 4, this dose level would be expanded to 6 patients. If no more than 1 subject experienced DLT at dose level 4, this will be the phase II recommended dose. Escalation beyond dose level 4 (everolimus 10 mg/day, the approved dose for everolimus monotherapy) was not planned. No intrapatient dose escalation was permitted.

Table 1 Dose escalation scheme (28-day cycle)

Dose level	RAD001 (days 1–21)	Cisplatin (days 1, 8, and 15)
1	2.5 mg PO/per PEG	20 mg/m^2 intravenously
2	5 mg PO/per PEG	20 mg/m^2 intravenously
3	7.5 mg PO/per PEG	20 mg/m^2 intravenously
4	10 mg PO/per PEG	20 mg/m^2 intravenously

PO per oral, *PEG*, percutaneous gastrostomy

Treatment plan

Everolimus (RAD001; Afinitor®) was supplied by Novartis Pharmaceuticals. Patients received weekly intravenous cisplatin (20 mg/m^2 intravenously over 30 min on days 1, 8, and 15) and daily oral everolimus (days 1 through 21 of a 28-day cycle) according to the dose escalation plan. For patients dependent on percutaneous gastrostomy tube, instructions were provided regarding administration of crushed everolimus tablets via the tube. One liter of intravenous normal saline was administered on each cisplatin day, as well as dexamethasone and aprepitant for emesis prevention. Patients were advised to take everolimus at the same time each day, either 1 h before or 2 h after eating. In March 2008, the protocol was amended to allow the option for subjects with objective radiographic response or stable disease after cycle 6 to transition to everolimus monotherapy (days 1 through 21 of a 28-day cycle) at the same dose. Patients who transitioned to everolimus monotherapy at any time after cycle 6 were not allowed to receive any more cisplatin on study. Patients were allowed to remain on study until progression of disease or unacceptable toxicity. Treatment response was assessed according to RECIST criteria, 2000 revised version [23].

Toxicity

Laboratory data (complete blood count, comprehensive metabolic panel including magnesium) regarding adverse events were collected on each cisplatin treatment day. Additional adverse event data were collected at regularly scheduled clinic visits at which history and physical were performed by the investigator (cycle 1—days 1, 8, 15, and 21; cycle 2—days 1 and 15; cycle 3 and beyond—day 1). Treatment was held for ≥grade 2 neutropenia, and dose reduction was required for any ≥grade 2 neutropenia lasting ≥7 days or any grade 4 neutropenia or febrile neutropenia. Treatment was held for platelets <75 × 10^9/L, and dose reduction was required for platelets <50 × 10^9/L. If creatinine clearance (CrCl) was <45 ml/min (Cockroft and Gault Method), treatment was held, and dose reduction was required if CrCl remained <45 ml/min for >7 days or if

CrCl < 35 ml/min. For other nonhematologic toxicities (not otherwise specified) ≥grade 3 (with the exception of grade 3 nausea or fatigue) or hematologic toxicities (not otherwise specified) ≥grade 4, treatment was held until the toxicity resolved to ≤grade 1. Treatment could be resumed at the next lower dose level if the toxicity improved to ≤grade 1. Treatment delay >7 days in cycle 1 or >21 days after cycle 1 would require removal from study.

Pharmacokinetics

Blood samples for pharmacokinetic (PK) analysis were collected on day 1 and 8 of cycle 1 only in the dose escalation portion of the study. Blood specimens (2 ml each) were collected at the following time points on cycle 1/day 1: 0, 15, 30, and 60 min; 2, 3, 4.5, 6, and 8 h. On cycle 1/day 8, an additional PK blood sample was collected prior to treatment with everolimus and cisplatin. Blood samples were collected in plastic tubes containing potassium EDTA, inverted several times immediately after collection, and frozen at −20°C or below within 60 min. Determinations of everolimus concentrations in whole blood were determined by a liquid chromatography and mass spectrometry at CRL Clinical Trials (Lenexa, Kansas). The area under the curve ($AUC_{0\rightarrow\infty}$), time to maximum concentration (t_{max}), and maximum concentration (C_{max}) for everolimus were determined by noncompartmental analysis.

Expansion cohort

After determination of the phase II recommended dose in the dose esclation portion of the study, there was an expansion cohort in which 6 additional subjects were treated at the phase II recommended dose. The expansion cohort allowed a larger safety experience with the combination of weekly cisplatin and everolimus and featured optional research biopsies for pilot pharmacodynamic studies. The expansion cohort did not include pharmacokinetics. Subjects in the expansion cohort were required to have tumor that was easily accessible for research biopsy. The phrase "easily accessible tumor" designates tumors that may be biopsied in an office setting with minimal risk of complication and discomfort to the patient.

Results

Patient characteristics and drug exposure

Thirty subjects were enrolled in study between January 2, 2007, and August 20, 2009. Twenty-four subjects enrolled in the dose escalation phase plus 6 subjects enrolled in the expansion cohort. Median age was 61 years, and most subjects were men (18 men, 12 women). The most common tumor types were head and neck squamous cell cancer (HNSCC, $n = 9$) and thyroid cancer ($n = 7$), and pulmonary carcinoid tumor ($n = 3$). Baseline characteristics are shown in Table 2.

Twenty-nine patients were treated, and one subject withdrew consent before receiving any study treatment. Median number of cycles administered was 2 (range, <1–22) in this population of patients with advanced cancers.

Dose escalation and adverse events

At dose level 1, one subject with a prior history of diverticulitis experienced recurrent diverticulitis during cycle 1, which resolved with conservative management. This was felt to be unrelated to study treatment, but the patient was removed due to >7 day delay in treatment, and the subject was replaced. Also at dose level 1, one subject with metastatic melanoma and extensive hepatic metastases died suddenly at home during the final week of cycle 1. The clinical impression was that death was related to progression of melanoma, but autopsy was not obtained and a contributory role for study drug in this grade 5 event could not be excluded. The cohort was expanded to 6 patients, and there were no further DLTs at dose level 1. Also in dose level 1, one enrolled subject with endometrial cancer withdrew consent before receiving any treatment, and one subject with colorectal cancer was removed during from study due to progression of disease during cycle 1. Both of these subjects were replaced.

At dose level 2, one patient with metastatic oropharynx cancer was admitted to hospital with small bowel obstruction, possibly due to disease progression. Treatment was held and the obstruction resolved with conservative management. A contributory role for study treatment could not be excluded as regards the small bowel obstruction, and the patient was removed from study. Dose level 2 was expanded to six patients without further DLT.

There were no DLTs among the first three subjects at dose level 3, and the study escalated to dose level 4. There were no DLTs among the first three subjects at dose level 4, and the cohort was expanded to six subjects to further evaluate if this would be the phase II recommended dose. Two subjects completed cycle 1 without DLT, and one subject withdrew consent during cycle 1 due to fatigue that was not felt to be dose-limiting. As such, the phase II recommended dose was dose level 4: everolimus 10 mg/day (days 1—through 21) and cisplatin 20 mg/m^2 (days 1, 8, and 15) of a 28-day cycle. For the expansion cohort, six additional subjects were enrolled at this dose level.

Twenty-eight patients were evaluable for toxicity; 1 patient was enrolled but withdrew consent prior to treatment, and 1 patient withdrew consent during cycle 1 and was deemed inevaluable. Table 3 lists adverse events that were

Table 2 Baseline characteristics

Characteristic	Summary
Number of subjects	30 subjects
Age, median (range)	61 years (31–79 years)
Gender (number male/number female)	18 subjects/12 subjects
Karnofsky performance status, median (range)	90 (70–90)
Prior chemotherapy	21 subjects
Prior radiotherapy	25 subjects
Tumor type	
Head and neck squamous cell cancer (HNSCC)	9[a] subjects
Thyroid cancer	7[b] subjects
Pulmonary carcinoid	3 subjects
Endometrial cancer	2 subjects
Basal cell carcinoma	2 subjects
Adenoid cystic carcinoma	2[c] subjects
Other	5[d] subjects

[a] Larynx ($n = 4$), oropharynx ($n = 3$), oral cavity ($n = 2$)

[b] Papillary ($n = 4$), hurthle cell ($n = 1$), medullary ($n = 2$)

[c] Breast ($n = 1$), head and neck ($n = 1$)

[d] Melanoma, sinonasal esthesioneuroblastoma, sinus carcinoma, colorectal adenocarcinoma, and nonsmall cell lung cancer, ($n = 1$ each)

felt to be at least possibly related to study treatment and occurred in at least 25% of subjects or were grade 3 or greater in more than two subjects. The most common adverse events were fatigue, low hemoglobin, and elevated glucose. The most common grade 3 adverse event was lymphopenia, but this did not appear to be clinically significant (Table 3).

Pharmacokinetics

Blood samples for pharmacokinetic (PK) analysis were collected on day 1 for all 23 subjects treated in the dose escalation phase of the study. The planned day 8 research blood sample was collected for 21 subjects. For each subject, t_{max}, C_{max}, and AUC of everolimus are shown in Table 4.

Although there was significant variability of PK results for everolimus between patients at a given dose level, there were dose-proportional increases in C_{max} (mean 91.9 ng/ml at dose level 4) and $AUC_{0\text{-}INF}$ (mean 680.5 h*ng/ml at dose level 4) (Table 5). Regarding the expansion cohort, optional research biopsy was attempted in only one subject, precluding meaningful analysis of tissue-based pharmacodynamic correlates.

Efficacy

There was evidence of efficacy among patients with head and neck cancer. At dose level 4, a 52-year-old woman was enrolled with a diagnosis of poorly differentiated carcinoma

Table 3 Summary of adverse events possibly related to study treatment

Adverse event	Any grade (%)	≥Grade 3 (%)
Fatigue	27 (96)	3 (11)
Low hemoglobin	24 (86)	2 (7)
Hyperglycemia	23 (82)	3 (11)
Leukopenia	19 (68)	0
Constipation	18 (64)	1 (4)
Thrombocytopenia	18 (64)	0
Hypercholesterolemia	16 (57)	0
Nausea	16 (57)	0
Elevated AST	15 (54)	2 (7)
Diarrhea	15 (54)	0
Cough	13 (46)	0
Hyponatremia	13 (46)	2 (7)
Elevated ALT	12 (43)	1 (4)
Hypomagnesemia	12 (43)	0
Oral mucositis, clinical	11 (39)	0
Hypertriglyceridemia	11 (39)	0
Lymphopenia	10 (36)	10 (36)
Elevated alkaline phosphatase	9 (32)	1 (4)
Neuropathy, sensory	9 (32)	0
Dyspnea	8 (29)	0
Epistaxis	8 (29)	0
Neutropenia	8 (29)	0
Hyperkalemia	8 (29)	2 (7)
Anorexia	7 (25)	0
Elevated creatinine	7 (25)	0
Functional mucositis	7 (25)	1 (4)
Headache	7 (25)	0
Rash	7 (25)	0
Venous thrombosis	3 (11)	3 (11)

of ethmoid sinus that had been initially treated with definitive radiation therapy with concurrent cisplatin. For metastatic disease identified seven months thereafter, she received radiation to sternum plus concurrent carboplatin and paclitaxel, and subsequently cetuximab. She experienced a partial response with everolimus plus cisplatin (best response: 41% reduction by RECIST) until progression of disease after 8 cycles. At dose level 4, a 63-year-old man with metastatic oropharynx cancer that had been pretreated (primary radiation plus concurrent cisplatin; gemcitabine plus pemetrexed for metastatic disease) experienced stable disease by RECIST criteria (19% reduction) until progression of disease at the end of cycle 4. In the expansion cohort, a 58-year-old man with recurrent oropharynx squamous cell carcinoma that had been extensively pretreated (induction docetaxel, cisplatin, 5-fluorouracil, radiation therapy with concurrent carboplatin; re-irradiation with

Table 4 Pharmacokinetics of daily everolimus administered with weekly cisplatin

Dose level	Pt. no.	AUC (h*ng/ml)	T_{max} (h)	C_{max} (ng/ml)
1	1	740.7	3.0	7.5
1	2	140.4	1.0	27.7
1	3	76.4	0.5	14.8
1	4	174.8	3.0	19.5
1	6[a]	67.5	0.5	13.1
1	7[b]	117.4	1.0	27.6
1	8	Not done[c]		
1	9	81.2	2.0	8.8
2	10	213.1	4.5	12.3
2	11[b,d]	174.7	0.5	48.0
2	12	136.1	0.5	40.8
2	13	337.7	1.0	68.9
2	14	326.4	1.0	29.9
2	15	261.3	3.0	38.9
3	16	249.1	1.0	35.5
3	17	354.9	1.0	53.8
3	18	414.5	2.0	82.0
4	19	353.9	0.5	76.5
4	20[b]	676.9	3.0	78.3
4	21	946.9	1.0	77.1
4	22	797.7	2.0	88.4
4	23	651.2	3.0	77.2
4	24	656.1	1.0	153.9

[a] Subject 5 was removed from study before receiving any treatment and was replaced. No PK data are available for subject 5 who had no exposure to everolimus

[b] Subjects 7, 11, and 20 were head and neck cancer patients with percutaneous gastrostomy tubes

[c] Data fail. No parameters could be extrapolated to infinity

[d] Subject 11 was the only study subject with detectable levels of everolimus in the sample labeled as time zero (27.8 ng/ml)

Table 5 Everolimus mean AUC and C_{max} at each dose level

Dose level	No. of patients	Mean AUC, h*ng/ml (SD)	Mean C_{max}, ng/ml (SD)
1	7[a]	199.8 (241.6)	17.0 (8.3)
2	6	241.5 (81.5)	39.8 (18.8)
3	3	339.5 (83.8)	57.1 (57.1)
4	6	680.5 (196.4)	91.9 (91.9)
All	22	361.3 (264.7)	49.1 (35.8)

[a] Nine subjects were enrolled at dose level 1, but subject 5 was removed from study before receiving any treatment. For subject 8, parameters could not be extrapolated to infinity (data fail). These two subjects are not included in the analysis for this table

concurrent cetuximab) experienced stable disease on study until progression of disease at the end of cycle 8. At dose level 1, a 64-year-old man enrolled with history of metastatic HNSCC that he been extensively pretreated (radiation therapy, gemcitabine, and pemetrexed) developed recurrent pulmonary emboli despite anticoagulation during cycle 2 and was removed from study. However, the CT scan that demonstrated the pulmonary embolus also documented minor regression of lung metastases (19% reduction, stable disease by RECIST).

Two patients with pulmonary carcinoid both at dose level 2 experienced major responses. A 48-year-old woman with atypical pulmonary carcinoid tumor with liver metastases that had been pretreated with cisplatin plus etoposide plus bevacizumab experienced a near complete response. After 10 cycles, she chose to transition to everolimus monotherapy and remained on study for approximately 1 more year until experiencing progression of disease. A 74-year-old man with atypical pulmonary carcinoid tumor with liver metastases, also previously treated with carboplatin plus etoposide plus bevacizumab, experienced partial response until progression of disease at the end of cycle 6. Also at dose level 2, a previously untreated 68-year-old man with advanced pulmonary carcinoid tumor experienced stable disease (9% reduction by RECIST) with reduced dyspnea and reduced cough, but developed progression of disease at the end of cycle 6.

Prolonged stable disease was experienced by one subject with recurrent sinonasal esthesioneuroblastoma that had been previously radiated (subject completed 22 cycles at dose level 2; 9 cycles of everolimus plus cisplatin, followed by 13 cycles of everolimus monotherapy). Additionally, one subject with advanced metastatic papillary thyroid cancer completed 14 cycles in the expansion cohort (everolimus monotherapy after cycle 6), and one subject with recurrent unresectable cutaneous basal cell carcinoma that had been previously radiated completed 6 cycles at dose level 1, both with stable disease.

Discussion

This phase I study demonstrates that the regimen of oral everolimus (10 mg/day, days 1–21) plus low-dose intravenous cisplatin (20 mg/m^2, days 1, 8, and 15 of 28-day cycle) is well tolerated as palliative therapy for patients with advanced solid tumors. The most common adverse events were fatigue, low hemoglobin, and elevated glucose. Pharmacokinetic analysis of everolimus demonstrated dose-proportional increases in C_{max} and $AUC_{0\text{-}INF}$. Evidence of anti-tumor efficacy with this regimen was observed in several tumor types.

The most common adverse events with this regimen were similar to those that have been previously described for everolimus monotherapy [15]. There were no episodes of >grade 2 neutropenia, and everolimus did not significantly intensify the relatively mild myelosuppression that

would be expected with low-dose weekly cisplatin. Although myelosuppression was generally mild, this study was not designed to evaluate whether mTOR inhibition might have a clinically significant impact on myelosuppression when combined with higher doses of cytotoxic chemotherapy.

Regarding other everolimus toxicities, hyperglycemia was mild for most patients and did not appear to be exacerbated in a clinically significant manner by dexamethasone that was given weekly as part of the anti-emetic regimen for cisplatin. We conjecture that weekly dexamethasone may have been protective against the small risk of interstitial lung disease that is associated with everolimus.

Everolimus PK results in this study were characterized by dose-dependent increases in AUC and C_{max}, with significant interpatient variability at each dose level. A priori, one would not predict a significant alteration in the PK profile of everolimus due to the concurrent administration of cisplatin, because cisplatin is renally cleared and everolimus is metabolized extensively by CYP3A4 [24]. The everolimus PK results in this study are consistent with those observed in subjects with advanced solid tumors treated with everolimus monotherapy [25].

Most of the tumors in this study were resistant to the study regimen. One potential mechanism of resistance may be paradoxical activation of Akt in tumors treated with rapamycin analogues. mTORC1 inhibition can result in enhanced phosphorylation of Akt^{Ser473} due to loss of negative feedback of S6 kinase on growth factor receptors, and other studies have demonstrated that paradoxical phosphorylation of Akt may be associated with resistance to rapalogues in some tumors [26, 27]. The development of agents that achieve upstream blockade of this pathway by inhibition PI3K or Akt may be an important research direction for tumors that are resistant to rapamycin analogues [28].

There were several efficacy signals with the current study regimen, suggesting that it merits further study. Two major responses were seen in subjects with pulmonary neuroendocrine tumors. Larger clinical studies could evaluate if the addition of low-dose weekly cisplatin enhances the established efficacy of everolimus against neuroendocrine tumors [16, 17].

There were also efficacy signals among several patients with advanced head and neck cancer in this study. In a phase Ib study of the mTOR inhibitor ridaforolimus plus weekly paclitaxel, a partial response was observed in a subject with squamous cell carcinoma of the pharynx that had been previously irradiated and pretreated with methotrexate [29]. The further study of mTOR inhibition in patients with head and neck cancer is also supported by the observation that these tumors demonstrate enhanced expression of proteins in the PI3K/Akt/mTOR pathway in a large international collaborative tissue microarray analysis [30]. Additionally, rapamycin inhibits tumor growth in a murine model of oral squamous cell carcinoma driven by mutant K-ras and p53 loss [31].

The study of mTOR inhibition may be particularly relevant among postoperative head and neck cancer patients with poor risk features on surgical pathology. Such patients are typically treated with adjuvant radiation therapy with concurrent high-dose cisplatin [32, 33], but there are also data to support the use of low-dose weekly cisplatin concurrent with radiation in the postoperative setting [34] and the latter approach may be better tolerated. Activation of the mTOR pathway in histologically negative surgical margins, resulting in increased expression of eIF4E, appears to be associated with increased risk of head and neck cancer recurrence [35, 36]. mTOR inhibitors have radiosensitizing properties preclinically [37, 38]. Taken together with the results of the current phase I study, these findings have motivated the development of an ongoing study of everolimus plus low-dose weekly cisplatin plus intensity-modulated radiation therapy (IMRT) for patients with head and neck cancer [39]. This combined modality regimen could merit further study in other tumor types for which cisplatin plus concurrent radiation therapy is commonly applied, such as cervical cancer and bladder cancer.

Because minimal toxicity was observed at dose level 4 in the current study, we anticipate that everolimus may be safely combined with higher doses of cisplatin-based chemotherapy. In follow-up to this study, our group also is conducting a phase I study of everolimus + docetaxel + cisplatin as induction chemotherapy in patients with locally and/or regionally advanced HNSCC [40]. In this ongoing study for previously untreated patients, cisplatin and docetaxel are both administered at 75 mg/m^2 (day 1 of a 21-day cycle) and dose escalation of everolimus is being explored.

In summary, the current study demonstrates the safety of oral everolimus (10 mg/day) given with weekly low-dose cisplatin on a 3 weeks on, 1 week off cycle. Adverse events were generally mild to moderate in this population of patients with advanced solid tumors. Pharmacokinetics of everolimus in this regimen appeared similar to those observed in studies of everolimus monotherapy. Efficacy signals suggest that this regimen merits further study in head and neck cancer and in advanced neuroendocrine tumors. The regimen also may be an attractive research option for further study in other tumors types in which cisplatin administration is a standard option and/or tumor types with aberrant activation of the PI3K/Akt/mTOR pathway.

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