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A Phase II study of oral mammalian target of rapamycin (mTOR) inhibitor, everolimus, in patients with recurrent endometrial carcinoma

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Abstract

Background—Dysregulation of PTEN and PIK3CA are the most common mutations in endometrial cancer (EC). Loss of PTEN or activation of PIK3CA results in constitutive activation of AKT, which leads to up-regulation of mTOR. Everolimus is an oral rapamycin analog that acts by selectively inhibiting mTOR.

Methods—A single institution, open-labeled, Phase II study of everolimus in patients with measurable recurrent EC who have failed at least one and no more than 2 prior chemotherapeutic regimens was performed. Everolimus was administered at a dose of 10 mg PO daily for 28-day cycles. Patients were treated until progression or toxicity. The primary endpoint was Clinical Benefit Response (CBR), defined as a confirmed complete or partial response or prolonged stable disease (SD ≥ 8 weeks). Inclusion was limited to patients with endometrioid histology.

Results—Thirty-five patients were enrolled (median age 58; range: 38–81). A total of 81 cycles were administered. Twelve of 28 (43%) evaluable patients did not progress at the first objective evaluation (8 weeks). All of these patients had SD (median: 4.5 cycles; range 2–10). Six of 28 (22%) had a confirmed CBR at 20 weeks of therapy. Patients with CBR discontinued treatment because of toxicity (6), progression (5), and noncompliance (1). Seven patients were inevaluable after receiving 1 cycle because of toxicity (5) or noncompliance (2). The most common drug related toxicities were fatigue, anemia, pain, lymphopenia, and nausea.

Conclusion—Everolimus showed encouraging single agent CBR in pretreated patients with recurrent endometrioid EC. Future studies will evaluate this agent in combination with hormonal and/or cytotoxic therapy.

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Introduction

In the United States, endometrial cancer remains the most commonly diagnosed gynecologic malignancy. While the majority of incident case will be cured with surgery alone or in combination with adjuvant therapy, over 8000 women die annually, predominately the a result of acquired resistance to conventional therapy. This observation has fueled intense investigation into alterative strategies, particularly those able to leverage an increasing knowledge into the molecular regulation of metastasis, proliferation and survival of tumor cells.

One such axis with broad appeal in many solid tumors, including endometrial cancer is the phosphatidylinositol-3-kinase/Akt pathway. Components of this pathway and its regulators are frequently constitutively activated or mutated promoting carcinogenesis. For instance, PTEN (phosphatase with tensin homology, which is located on chromosome 10), a tumor suppressor gene regulating activation of Akt from PI3K is absent or inactivated by mutation in 40–80% of endometrial cancers and PIK3CA, the gene which encodes the p110 α catalytic subunit of PI3K can undergo gain-of-function mutation in 39% of endometrial cancers (1–4). Downstream effects include hyperactivation of Akt (5) and, in turn, its downstream effector proteins including the mammalian target of rapamycin (mTOR). mTOR acts as a sensor that integrates extracellular and intracellular events, coordinating growth and proliferation. mTOR is an intracellular protein kinase implicated in cell cycle control and specifically in the progression of cells from G1 to S phase.

Rapamycin and its derivatives inhibit the function of mTOR. Preclinical studies have revealed that mTOR inhibitors potently arrests growth of cells derived from rhabdomyosarcoma, neuroblastoma, glioblastoma, small cell lung cancer, osteosarcoma, pancreatic, breast, and prostate cancer, melanoma, leukemia, and lymphoma (6). In endometrial cancer cell lines, rapamycin demonstrated a growth-inhibitory effect through induction of cell cycle arrest (7), and rapamycin inhibited phosphorylation of downstream targets of mTOR (S6K and 4E-BP1). In PTEN heterozygote animal models, mTOR inhibition decreases the development and progression of endometrial hyperplastic lesions (8, 9). These effects are due primarily to decreased cellular proliferation and increased apoptosis.

The purpose of this study was to evaluate the benefit of everolimus (Afinitor™, Everolimus, RAD001, Novartis Pharma, Basel, Switzerland) in the treatment of women with previously treated endometrial cancer. The primary efficacy endpoint is Clinical Benefit Response (CBR), defined as a confirmed complete or partial response or prolonged stable disease (SD; 8 weeks) by RECIST criteria.

Patients and Methods

This was a phase II open labeled trial conducted at University of Texas MD Anderson Cancer Center. Everolimus was kindly provided by Novartis Pharma (Basel, Switzerland). This study is registered on the clinical trial website of the National Cancer Institute (clinicaltrials.gov, NCT00087685). Institutional review board approval was obtained.

Patient Population

Patients with progressive or recurrent endometrial cancer who had received one or two prior chemotherapeutic regimens were entered into this investigator initiated phase II trial. Eligible patients had to have histologically-confirmed endometrioid endometrial adenocarcinoma. Patients with serous, clear cell, carcinosarcoma, sarcoma, or other histologic subtypes were excluded. Patients were required to have a Zubrod performance status 0–2 and no history of an invasive malignancy other than endometrial cancer within a 5 year period prior to trial entry. Patients were required to have measurable disease (defined as lesions equal to or greater than 2 cm in at least one dimension when evaluated by physical exam, or conventional radiographic imaging or equal to or greater than 1 cm in at least one dimension when evaluated by spiral computed tomography (CT)). Ascites and pleural effusions were not considered measurable disease.

No prior treatment with an mTOR inhibitor was allowed. No concomitant anti-cancer treatment was allowed. Patients with active infections were excluded. Pretreatment hematologic, renal, and hepatic function tests were required to be CTCAE v3.0 grade 0 or 1.

Pretreatment evaluation included a physical exam, assessment of performance status, measurement of index lesion (s) for response assessment clinically or via CT scan, chest x-ray, or MRI, and hematologic and biochemical blood tests. Other testing was performed at the physician discretion. Written informed consent was obtained from all patients before trial entry.

Treatment plan and response evaluation

All patients were treated on an outpatient basis and were treated until progression, dose limiting toxicity or confirmed complete clinical response. All patients were started on an oral dose of 10 mg daily. One dose reduction was allowed for grade 2 or higher hematologic or non-hematologic toxicity. One cycle of therapy was considered 4 weeks.

Records of study medication used, dosages administered, and intervals between visits were kept during the study. Drug accountability was by the study coordinator during the study and at the completion of the trial.

The primary efficacy endpoint is Clinical Benefit Response (CBR), defined as a complete or partial response or prolonged stable disease (SD; 8 weeks) by RECIST criteria. Response was defined according to Response Evaluation Criteria in Solid Tumors (RECIST v1.0) criteria. Follow-up imaging for all patients not demonstrating progressive disease at the initial clinical evaluation time point (8 weeks) was performed every 12 week thereafter. Patients were evaluated sooner if they demonstrated obvious progression by physical exam, clinical deterioration or new symptomatology suggestive of clinical progression. We confirmed the previous best response to therapy by these subsequent imaging studies. As long as the tumor was stable or smaller in size and the patient was clinically stable, treatment would continue. A secondary endpoint was to determine the nature and degree of toxicity of everolimus in this cohort of patients. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria (NCI CTC v3.0). A grade 2 or higher toxicity

required treatment to be held until recovery to at least a grade 1 toxicity. Response duration was measured from the time measurement criteria were first evaluated until progression.

Statistical Considerations

This study incorporated a Bayesian design with multiple early stopping points. The target clinical benefit rate was 20%. CBR was evaluated as patients were accrued, and the trial was to be stopped if there was evidence that the target CBR rate cannot be met. That is, given the outcomes from the patients who have already been evaluated, if we determined that there was less than a 10% chance that the CBR rate was 20% or more, the trial would have been stopped.

Results

Patients

Thirty-five patients were enrolled in the trial between January 2004 and December 2007. Median patient age was 58 years (range: 38 – 81). Study subjects received a total of 81 cycles of therapy. Median time since prior chemotherapy was 3 months (2–19 months). All 35 women were evaluable for toxicity; 28 were evaluable for response. Seven patients were inevaluable after receiving 1 cycle because of toxicity (n=5) or noncompliance (n=2). Baseline characteristics of the enrolled patients are listed in Table 1.

Efficacy

Of the 28 evaluable patients, 12 (43%) had not demonstrated progression at the first evaluation assessment. There were no complete or partial responses. The median duration of SD was 4.5 months (range 2 –10). Patients with SD discontinued treatment because of toxicity (n=6), progression (n=5), and noncompliance (n=1). The confirmed CBR rate (imaging at 20 weeks of treatment) was 22% (6/28). Of these 6 patients, 3 were discontinued for progressive disease, 2 patients developed treatment related pulmonary toxicity and 1 patient developed recurrent grade 3 neutropenia.

Safety

The safety population of 35 patients included all patients who received at least one dose of the study drug. Seventeen patients (49%) required dose reduction to 5 mg daily because of stomatitis (n=10), hyperglycemia (n=3), thrombocytopenia, hypertriglyceridemia, rash and fever. The most common adverse events considered possibly, probably, or definitely related to everolimus were fatigue, anemia, pain, lymphopenia, and nausea (Table 2).

Discussion

In this Phase II study of everolimus for the treatment of patients with recurrent or persistent endometrioid endometrial cancer, we have demonstrated a relatively high rate of stable disease to monotherapy with this oral agent.

Oza and colleagues from the National Cancer Institute of Canada evaluated CCI-779 (temsirolimus, Torisel™, Wyeth Pharmaceuticals) in patients with untreated (1st line)

metastatic or recurrent endometrial cancer (10). Temsirolimus is an mTOR inhibitor available in an intravenous formulation. In their study, there was a 25% partial response (median 5.1 months) and a 57% stable disease rate (median 8.7 months). There was no correlation between biologic markers (including PTEN) and response. Their population included patients with serous and clear cell histologies in addition to the endometrioid histology. At the 2008 ASCO meeting, the same group presented data in pre-treated patients, similar to our population. Two patients or 7% had a partial response and 44% had stable disease for a median of 3.5 months (11).

Another mTOR inhibitor, AP23573 (deforolimus) was also studied in a multi-site trial of 45 patients with recurrent endometrial cancer. These investigators found a 7% partial response and 26% stable disease rate. In most of the responders, the duration of response was less than 4 months (12). See Table 3 for a summary of these data.

In this study, patients with histologic subtypes other than endometrioid were excluded. The rationale for these criteria were based on the presence of PTEN mutations primarily in the endometrioid tumors. The other studies of mTOR inhibition in patients with recurrent endometrial cancer include all histologic subtypes and clinical benefit has been demonstrated in patients with these other types. We are conducting further translational studies in our group of patients to determine if PTEN mutational status is predictive of response. Future studies of mTOR inhibition will likely not exclude endometrial cancers based on histology.

The safety profile of everolimus was acceptable in the context of heavily pretreated patients with endometrial cancer. When the trial was initiated, initiation of lipid lowering drugs for patients who developed grade 2 or greater hypertriglyceridemia or hypercholesterolemia was not allowed. Since the initiation of this trial, mTOR inhibition has been associated more strongly with these abnormalities. In this study, 17% of patients had elevated cholesterol and 14% had elevated triglycerides. Three patients with stable disease were removed because of these abnormalities. Future studies of everolimus should include a treatment modification to add a statin therapy in the setting of grade 2 or higher lipid abnormalities. Two patients with stable disease experienced pulmonary toxicity requiring withdrawal from study. Both of these patients were on therapy for a prolonged time (6 and 10 months). After discontinuation of treatment, toxicities resolved spontaneously. This pulmonary related toxicity needs to be further evaluated in patients on prolonged mTOR inhibitor therapy.

While our findings are encouraging and suggest activity similar to that found in the evaluation of other mTOR inhibitors, further investigation is needed to evaluate the role of mTOR inhibition in the treatment of this disease. Potential benefits of everolimus are its oral bioavailability and its relatively favorable toxicity profile. In addition, while combination therapy may be a more attractive (and effective) alternative, it is unclear which type of therapy (i.e., hormonal, cytotoxic, radiation) should be combined with everolimus or other mTOR inhibitors.

The Gynecologic Oncology Group is initiating a phase II trial of carboplatin and paclitaxel in combination with temsirolimus as first line therapy in patients with untreated recurrent or

progressive endometrial cancer. MD Anderson Cancer Center is opening a similar trial of carboplatin and paclitaxel in combination with everolimus in the same population of patients. We have also initiated a phase II trial of everolimus in combination with letrozole for the treatment of patients with previously treated recurrent or progressive endometrial cancer. This combination has been evaluated as part of a neoadjuvant breast cancer trial (13). In that trial, everolimus significantly increased the efficacy of letrozole in patients with ER positive breast cancer. The frequent expression of hormonal receptors in endometrial cancer, particularly in lower grade lesions suggests a similar strategy may be relevant in this disease.

The statistical design of the study incorporated stable disease at 8 weeks for minimal criteria for meeting CBR. All of the 12 patients who were considered to have stable disease were underwent a radiological assessment at no earlier than 8 weeks. In order to confirm this single agent activity, patients were reassessed after an additional 3 cycles (12 weeks) of therapy. Over 20% of patients in this cohort who are heavily pretreated demonstrated a confirmed CBR after 20 weeks of treatment.

In conclusion, mTOR inhibition with the oral agent everolimus in patients with recurrent endometrioid endometrial cancer demonstrates clinical benefit. While achieving disease remission while on single agent therapy is not likely, limiting disease growth by interrupting this key biologic pathway is a reasonable approach for disease control. We have trials underway which will evaluate the role of combination therapy with aromatase inhibition and with cytotoxic therapy.

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Table 1

Demographic summary

Age	
Median	58
Range	38–81
Stage	
I	9
II	4
III	11
IV	6
Unstaged	5
Prior Radiation	
Total	22
Pelvic +/- vaginal brachytherapy	17
Vaginal brachytherapy alone	3
Palliative	2
Prior chemotherapy (Number of prior regimens)	
0	1
1	18
2	14
3	2
Prior hormonal/other therapy	
Megace	5
Aromatase inhibitor	2
Tamoxifen	1
Bevacizumab	1

Table 2

Adverse events considered possibly, probably, or definitely related to everolimus

	Overall		Grades 3 to 4	
	N	%	N	%
Acne	5	17	0	0
Anorexia	4	13	1	3
Chills	5	17	1	3
Constipation	7	23	0	0
Dehydration	1	3	1	3
Diarrhea	6	20	1	3
Dry skin	2	7	0	0
Dyspnea	6	20	0	0
Dysuria	1	3	0	0
Fatigue	19	63	12	40
Headache	7	23	3	10
Hearing loss	3	10	0	0
Hematoschezia	1	3	1	3
Hematuria	1	3	1	3
Hypotension	3	10	0	0
Injection site rxn	1	3	0	0
Leg edema	2	7	2	7
Mood changes	1	3	0	0
Motor neuropathy	1	3	1	3
Mucositis	5	17	0	0
Muscle weakness	1	3	1	3
Nausea	10	33	1	3
Pain (all sites)	7	23	3	10
Pneumonia	1	3	1	3
Sensory neuropathy	2	7	2	7
Sweating	4	13	0	0
Vomiting	7	23	2	7
Weight loss	1	3	0	0
Anemia	6	20	0	0
Thrombocytopenia	1	3	1	3
Bilirubin	1	3	1	3
Hyponatremia	1	3	1	3

Table 3

Summary of mTOR inhibitors studied in endometrial cancers

Agent	N	Population	RR [#]	CBR [^]	Duration
Temsirolimus (10)	19	No prior therapy	25%	82%	8.7 mos
Temsirolimus (11)	27	1 prior regimen	7%	51%	3.5 mos
Deferolimus (12)	45	Up to 2 prior regimens	7%	33%	< 4 mos
Everolimus (Current Study)	35	1 or 2 prior regimens	0%	43%	4.5 mos

[#]RR: Response Rate = complete response (CR) + partial response (PR)

[^]CBR: Clinical Benefit Rate = (CR + PR + SD)