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Temsirolimus with or without megestrol acetate and tamoxifen for endometrial cancer: A gynecologic oncology group study

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HIGHLIGHTS

- The combination of hormone therapy plus temsirolimus did not improve response rates compared to temsirolimus alone.
- The combination of therapy with megestrol acetate/tamoxifen plus temsirolimus resulted in a 33% rate of venous thrombosis.
- Two of four patients with clear cell carcinoma of the endometrium responded to temsirolimus.

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ABSTRACT

Objectives. To determine the response, toxicities, and progression free survival of a regimen of temsirolimus with or without hormonal therapy in the treatment of advanced, or recurrent endometrial carcinoma.

Background. Preclinical evidence suggested that blockade of the PI3K/AKT/mTOR pathway might overcome resistance to hormonal therapy.

Methods. We performed a randomized phase II trial of intravenous temsirolimus 25 mg weekly versus the combination of weekly temsirolimus with a regimen of megestrol acetate 80 mg bid for three weeks alternating with tamoxifen 20 mg bid for three weeks in women with recurrent or metastatic endometrial carcinoma.

Results. There were 71 eligible patients who received at least one dose of therapy with 21 of these treated on the combination arm which was closed early because of an excess of venous thrombosis, with 5 episodes of deep venous thrombosis (DVT) and 2 pulmonary emboli. There were three responses observed in that arm (14%). A total of 50 eligible patients were treated on the single agent arm with 3 episodes of DVT and 11 responses (22%). Response rates were similar in patients with prior chemotherapy (7 of 29; 24%) and those with no prior chemotherapy (4 of 21; 19%). Two of four patients with clear cell carcinoma responded.

Conclusions. Adding the combination of megestrol acetate and tamoxifen to temsirolimus therapy did not enhance activity and the combination was associated with an excess of venous thrombosis. Temsirolimus activity was preserved in patients with prior adjuvant chemotherapy.

Introduction

Advanced or recurrent endometrial carcinoma is an incurable disease with short overall survival. Standard initial therapy for many

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years consisted of treatment with medroxyprogesterone acetate or megestrol acetate, and response rates of 15%–27% to progestin-based regimens in chemotherapy-naïve patients have been published by a number of authors [1,2]. However the median progression-free survival with such regimens is short, and although low-grade and estrogen or progesterone receptor-positive tumors have higher response rates to endocrine therapy, no reliable predictive factors for benefit have emerged [3]. Currently, most women with advanced disease are initially treated with platinum/taxane-based chemotherapy. Such regimens yield response rates in the range of 50%, but the median survival remains only about 12–15 months [4].

As targeted agents began to show promise in a number of different tumor types, interest was focused on the high frequency of aberrations in the PI3K/Akt/mTOR pathway in endometrial cancers [5]. A number of mTOR inhibitors have been tested in endometrial cancer and found to have only modest activity (Table 1). Phase II studies of temsirolimus conducted by the National Cancer Institute of Canada (NCIC) showed a 14% response rate in chemotherapy-naïve patients and a 4% response rate in patients with prior chemotherapy [6].

In endometrial cancer cell lines and mouse models, upregulation of PI3K/Akt/mTOR pathway activity is associated with resistance to progestin therapy, and inhibition of the pathway can reverse this resistance [7,8]. Similar observations have been made regarding the association of resistance to tamoxifen and aromatase inhibitors with PI3K/Akt/mTOR pathway activity in breast cancer models. These led to a phase III trial in which breast cancer patients previously treated with a nonsteroidal aromatase inhibitor who were randomized to the combination of the mTOR inhibitor, everolimus, plus exemestane had significantly superior progression-free survival compared to those randomized to exemestane alone [9].

We therefore performed a randomized open-label two-stage phase II trial of temsirolimus alone versus the combination of temsirolimus plus a hormonal therapy regimen consisting of alternating megestrol acetate and tamoxifen. This hormonal therapy was chosen based on data published by the Gynecologic Oncology Group (GOG) showing a response rate of 27% and a median response duration of 28 months with the regimen [2]. While there are no data showing that such a regimen is superior to single agent progestin therapy, regimens including periodic tamoxifen have produced the highest response rates in the GOG experience. Archival tumor tissue was collected and stained for ER, PR, PTEN, and phospho-AKT.

Patients and methods

Eligibility

Subjects were required to have measurable endometrial carcinoma (RECIST version 1.0) that was either stage III or IV, or persistent or recurrent after treatment for earlier stage disease. Prior endocrine therapy was prohibited; up to one prior chemotherapy regimen was allowed, but if that regimen was administered in the setting of stage IV disease it was required that the patient have been without evidence of disease at the completion of chemotherapy and have had at least six months of progression-free survival since the completion of chemotherapy.

Table 1
Trials of single-agent mTOR inhibitors in endometrial cancer.

Author	Agent	Prior chemotherapy regimens	RR
0za et al. [17]	Temsirolimus	None	14%
0za et al. [17]	Temsirolimus	1–2	4%
Slomovitz et al. [19]	Everolimus	1–2	0
Ray-Coquard et al. [33]	Everolimus	1–2	5%
Colombo et al. [34]	Ridaforolimus IV	0–2	11%
Mackay et al. [35]	Ridaforolimus PO	Adjuvant only	7.7%
0za et al. [29]	Ridaforolimus	1–2	0

RR = response rate; IV = intravenous; PO = per os (orally).

Chemoradiotherapy was counted as a chemotherapy regimen. Other eligibility criteria included performance status 0–2, absolute neutrophil count ≥1500/mcl, platelets ≥100,000/mcl, total bilirubin ≤ institutional upper limit of normal (ULN), AST and alkaline phosphatase ≤2.5 times ULN (≤5 times ULN for subjects with liver metastases), creatinine ≤1.5 times ULN, fasting cholesterol ≤350 mg/dL, fasting triglycerides ≤400 mg/dL, and albumin ≥3.0 mg/dL. Long term corticosteroid use as well as enzyme-inducing antiepileptic drugs and other CYP3A4 inducers were prohibited. Patients with known congestive heart failure or a need for oxygen use were excluded, as were those with a history of unprovoked deep venous thrombosis (DVT) or pulmonary embolus (PE), unless maintained on anticoagulation for the duration of the trial. All subjects signed an institutionally approved informed consent including HIPAA authorization. Central review of the initial pathologic diagnosis by the GOG Pathology Committee was performed for all cases.

Study design and treatment plan

Treatment was randomly assigned with equal probability within strata as either single agent temsirolimus at a dose of 25 mg intravenously (IV) weekly or the combination of temsirolimus 25 mg IV weekly plus megestrol acetate 80 mg orally twice a day for 3 weeks alternating with tamoxifen 20 mg orally twice a day for 3 weeks. Randomization was stratified on the basis of prior chemotherapy (yes or no). After closure of the combination arm, accrual to single agent temsirolimus therapy continued. A letter describing the risk of thrombosis was sent to physicians and patients on the combination therapy arm, and they were allowed to choose whether to remain on their current regimen, receive temsirolimus alone, or to discontinue protocol-directed therapy. Therapy was to be continued until tumor progression or undue toxicity.

Management of toxicity

Administration of subsequent doses of temsirolimus required ANC greater than or equal to 1000/mcl and platelets greater than or equal to 100,000/mcl. Temsirolimus was held until these parameters were met and restarted with a 5 mg dose reduction. Tamoxifen and megestrol acetate could be continued while temsirolimus was held. Subjects experiencing a venous thrombotic event were permitted, at the discretion of the investigator, to stay on study with institution of therapeutic anticoagulation. Toxicities requiring cessation of treatment included: grade 2 or higher pneumonitis, requirement for a dose reduction of temsirolimus to less than 15 mg, and grade 3 or 4 toxicities requiring over 14 days till recovery to tolerable grade 2 or better.

Evaluation

Toxicity was graded according to CTCAE version 3.0. Re-evaluation for disease response was performed every six weeks for the first 24 weeks of therapy, and then every 12 weeks. RECIST criteria version 1.0 were used for assessment of response. The categories of confirmed, complete and partial response were combined to define tumor response. Progression-free survival (PFS) was defined as the time from study entry to death or documentation of disease progression. Patients alive with no evidence of disease progression were censored at the time of their last follow-up. Survival (OS) was defined as the time from study entry to death, regardless of cause; patients last known to be alive were censored at the time of last follow-up.

Immunohistochemical analysis

Formalin-fixed, paraffin-embedded (FFPE) tissue sections were sent to the GOG Tissue Bank and distributed to the GOG Core Laboratory for Receptors and Targets. Before starting the experiments, immunostaining protocols and antibody dilution for estrogen receptor-alpha (ER; Dako, Carpinteria, CA), progesterone receptor (PR; Dako, Carpinteria, CA),