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Phase II study of temsirolimus (CCI-779) in women with recurrent, unresectable, locally advanced or metastatic carcinoma of the cervix. A trial of the NCIC Clinical Trials Group (NCIC CTG IND 199)☆,☆☆

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HIGHLIGHTS

- This phase II clinical trial studied the activity of temsirolimus, an mTOR inhibitor, in advanced/recurrent/metastatic cervical cancer.
- Response rates were low, however the rates of disease stability and 6 month progression free survival rates were notable.
- Molecular correlates of the AKT/mTOR pathway correlating with disease stability were not identified using archival tumour tissue.

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ABSTRACT

Objective. HPV infection has been associated with deregulation of the PI3K-Akt-mTOR pathway in invasive cervical carcinomas. This 2-stage phase II study assessed the activity of the mTOR inhibitor, temsirolimus, in patients with measurable metastatic and/or locally advanced, recurrent carcinoma of the cervix.

Methods. Temsirolimus 25 mg i.v. was administered weekly in 4 week cycles. One response among the first 18 patients was required to proceed to the second stage of accrual. Correlative molecular studies were performed on archival tumor tissue.

Results. Thirty-eight patients were enrolled. Thirty-seven patients were evaluable for toxicity and 33 for response. One patient experienced a partial response (3.0%). Nineteen patients had stable disease (57.6%) [median duration 6.5 months (range 2.4–12.0 mo)]. The 6-month progression free survival rate was 28% (95% CI: 14–43%). The median progression free survival was 3.52 months [95% CI (1.81–4.70)]. Adverse effects were mild–moderate in most cases and similar to other temsirolimus studies. No toxicity > grade 3 was observed. Assessment of PTEN and PIK3CA by IHC, copy number analyses and PTEN promoter methylation status did not reveal subsets associated with disease stability.

Conclusion. Single agent temsirolimus has modest activity in cervical carcinoma with about two-thirds of patients exhibiting stable disease. Molecular markers for treatment benefit remain to be identified.

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Introduction

Globally, carcinoma of the cervix is the second most common malignancy in women after breast cancer. Approximately 200,000 women worldwide die from this disease each year [1]. Most patients with cervical cancer are candidates for potentially curative treatment using primary radiotherapy and concurrent platinum-based chemotherapy, however, a significant proportion of patients will recur and die [2]. Patients with advanced disease not amenable to curative

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loco-regional therapy or those with recurrent disease have a poor prognosis with a median survival of only 9 months [3].

Response to single agent cisplatin lies between 20 and 30%. Platinum based combination regimens demonstrate higher response rates but these have not translated into a meaningful survival benefit [3–5], and median overall survival remains less than 12 months. Response to second line therapy is low and of unproven benefit compared to best supportive care. The outlook for patients with recurrent or advanced cervical cancer is very poor and novel therapeutic strategies are urgently required.

mTOR inhibitors are of interest in cervical cancer because the mTOR pathway is frequently activated in cervical carcinomas. mTOR activation has been linked to HPV infection, the causative factor for nearly all cervical cancers. Multiple aberrations of the mTOR pathway have been reported in cervical cancer, including overexpression of phosphatidylinositol 3-kinase (PI3K) [6] and of phosphorylated mTOR as well as the downstream regulators, p70S6 kinase (P70S6K) [7] and eukaryotic initiation factor 4E binding protein (4EBP1) [8]. When phosphorylated by mTOR, P70S6K and 4EBP1 may enhance translation of mRNAs encoding proteins involved in cell growth/size and cell cycle progression [8]. HPV-encoded oncoproteins E5, E6 and E7 promote cell replication and immortalization. E6 also interacts with and degrades the tuberous sclerosis complex 2 (TSC2), which can lead to enhanced mTOR activity [9]. The potential role of mTOR in cervical cancers is further supported by the in vitro observation that inhibition of mTOR activity blocks cervical cancer cell growth [6,10,11]. Therefore, therapeutic targeting of mTOR is rational in this disease.

Targeting the PI3K/AKT/mTOR pathway has emerged as a promising therapeutic strategy in several cancers. The rapalogs, a class of agents which include temsirolimus (CCI-779), target the mTOR pathway by partially inhibiting MTORC1 (part of the MTOR complex), and have demonstrated clinical efficacy, as well as generally favorable toxicity profiles. They have been approved for the treatment of advanced renal cell carcinoma [12,13] mantle-cell lymphoma [14] and are indicated for the management of advanced pancreatic neuroendocrine tumors [15]. Temsirolimus toxicity is typically low grade and includes mucocutaneous toxicity (i.e. mucositis, rash, and diarrhea) as well as fatigue, anorexia, neutropenia, thrombocytopenia, hyperglycemia, and hyperlipidemia.

Given the interaction between HPV infection and the mTOR/PI3K pathway, we conducted a two-stage, multi-center, phase II study to evaluate the activity and safety of temsirolimus in patients with unresectable, locally advanced or metastatic cervical carcinoma.

Methods

This two-stage, multi-center, phase II study was conducted by the NCIC Clinical Trials Group (NCIC CTG). Good Clinical Practice guidelines were adhered to and full research ethics board (REB) approval was obtained at each participating center prior to patient enrollment. All patients signed the REB-approved written informed consent before study entry.

Eligibility

Patients with histologically confirmed metastatic/unresectable, locally advanced squamous cell, adenosquamous or adenocarcinoma of the cervix, incurable by standard therapies were considered for this trial. In order to be eligible, tissue blocks from primary tumor had to be available. Up to one prior line of chemotherapy for recurrent or metastatic disease was permitted (primary chemoradiation using cisplatin was not considered as a line of therapy). Additional eligibility criteria included: age $\geq$ 18 years; life expectancy $\geq$ 12 weeks; Eastern Cooperative Group (ECOG) performance status $\leq$2; adequate hematologic; hepatic and renal function; the presence of clinically or radiologically measurable disease (as per RECIST criteria v. 1.1 [16]); and palliative radiotherapy completed >4 weeks before study entry. Reasons for exclusion included: previous treatment with an mTOR inhibitor, any history of other malignancy (except adequately treated non-melanoma skin cancer, or other solid malignancy curatively treated without recurrence for $\geq$5 years); a history of/or known brain metastases; clinically significant cardiovascular disease; pregnancy or breastfeeding; or a serious medical condition or illness which would interfere with protocol adherence. Carefully monitored therapeutic anti-coagulation was permitted. Concurrent treatment with other anti-cancer therapies or investigational drugs was not permitted.

Study design and treatment

Temsirolimus was delivered as a 30 minute intravenous infusion on a weekly basis (days 1, 8, 15, and 22) at a starting dose of 25 mg. Four weeks of therapy constituted one cycle. Cycle length was not changed if doses were missed. Patients were monitored for toxicity and up to two dose reductions were permitted: dose level −1, 20 mg; dose level −2, 15 mg. Treatment was continued until disease progression (or a maximum of 12 cycles), unacceptable adverse event(s), patients' decision to withdraw from the study, or inability to continue treatment.

Evaluation of toxicity and tumor response

Baseline evaluations included medical history, physical examination, and laboratory tests (hematology, coagulation, standard blood chemistry, urine pregnancy test) and were performed within 7 days of registration. Tumor imaging with CT scan of the chest, abdomen and pelvis was obtained within 21 days of registration. Blood pressure, heart rate, and hematologic and biochemical monitoring occurred weekly for cycle 1 and on day 1 of each cycle thereafter (hematology required bi-weekly). Evaluation of toxicity according to NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3 was performed on day 1 of each cycle. Tumor response was evaluated with imaging every second cycle (8 weeks).

Statistical methods and endpoints

The primary endpoint of this study was the objective response rate as determined by RECIST criteria version 1.1 [16]. Secondary endpoints included evaluation of toxicity, early progression rate and response duration. Stable disease duration was calculated only for patients whose best response was stable disease. Progression free survival was calculated for all eligible patients as the time from randomization to the time when disease progression or death was observed or censored at the last disease assessment or when other treatment started. The protocol planned to accrue up to 32 response-assessable patients. A Simon optimal two-stage design was used to determine sample size and stopping rule [17]. In the first stage, 18 response-assessable patients would be entered. Using response hypotheses of H0 no greater than 5% and Ha of at least 20%, the drug would be rejected at the end of the first stage of accrual if no responses were seen. If at least one response was seen, an additional 14 patients, for a total of 32 patients, would be accrued in the second stage. The drug would be accepted as active if four or more responses were observed in the 32 patients accrued. The significance level of this design was $\alpha = 0.07$ when the true response rate is 5% and the power was 0.90 when the true response rate is 20%.

Molecular correlative studies

A representative archival sample of formalin fixed paraffin embedded (FFPE) diagnostic tissue was obtained from all patients at the time of study enrolment for assessment of PTEN and PIK3CA expression, copy number and methylation studies as outlined below.

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