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A phase I study of temsirolimus and thoracic radiation in non-small cell lung cancer

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Abstract

Background—The addition of targeted agents to thoracic radiation has not improved outcomes in patients with locally advanced non-small cell lung cancer (NSCLC). In order to improve cure rates in locally advanced NSCLC, effective targeted therapies need to be identified that can be given safely with radiation therapy. Temsirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) pathway and has single agent activity in lung cancer. Inhibition of the mTOR pathway has been shown to augment the cytotoxic effect of radiation in preclinical studies. There is scant clinical experience with mTOR inhibitors and radiation.

Methods—We performed a phase I study evaluating the combination of temsirolimus with thoracic radiation in patients with NSCLC.

Results—Ten patients were enrolled in the study. The dose limiting toxicities included sudden death, pneumonitis and pulmonary hemorrhage. The maximum tolerated dose of temsirolimus that could be administered safely with concurrent radiotherapy (35 Gy in 14 daily fractions) was 15 mg intravenously weekly. Of the 8 evaluable patients, 3 had a partial response and 2 had stable disease.

Conclusion—The combination of temsirolimus 15 mg weekly and thoracic radiation is well-tolerated and warrants further investigation, perhaps in a molecularly defined subset of patients.

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Introduction

Approximately 26% of patients with non-small cell lung cancer (NSCLC) present with locally advanced disease which is not amenable to surgical resection.[1] Concurrent administration of systemic chemotherapy along with thoracic radiation has been shown to improve survival over thoracic radiation alone in several randomized studies.[2,3] However, even with the use of modern chemotherapy regimens and state of the art radiation techniques, the 3 year survival rate is at best only 30%.[2,4] Moreover, concurrent chemoradiation is associated with significant toxicities including esophagitis and febrile neutropenia, and therefore considered only in the first line, potentially curative setting for patients with good performance status. While thoracic radiation alone is associated with fewer toxicities, 3 year survival is only 11%, largely due to distant relapse.[5] Two large trials one exploring the substitution of pemetrexed for etoposide, and the other investigating the role of higher than conventional doses of thoracic radiation unfortunately have failed to improve overall survival in patients with locally advanced NSCLC.[6,7] The addition of targeted agents to thoracic radiation thus far has not been successful.[8,9] The only way to improve outcomes in patients with locally advanced NSCLC is to use targeted therapies in molecularly selected patients who receive chemoradiation.

Activation of the mammalian target of rapamycin (mTOR) pathway has been implicated in the development of several malignancies, including lung cancer.[10,11] A member of the phosphatidylinositol 3-kinase (PI3K)-related family of kinases, mTOR is a 289-kDa protein serine/threonine kinase that was first identified as the cellular target of rapamycin and is involved in checkpoint regulation of the cell cycle regulation. Additionally, the mTOR pathway is responsible for upregulating downstream signaling of hypoxia inducible factor-1-α (HIF1-α) which promotes angiogenesis and cell proliferation.[12] Temsirolimus is an inhibitor of the mTOR kinase and has demonstrated anti-proliferative and anti-angiogenic activity in multiple tumor types. Temsirolimus has been approved in the treatment of renal cell carcinoma, and is generally well-tolerated with observed grade 3 or 4 toxicities of temsirolimus including hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridemia (6%).[13,14] In the phase II study reported by Ruengwetwattana and colleagues, 55 patients with untreated NSCLC were treated with temsirolimus 25 mg intravenously on a weekly basis.[15] The clinical benefit rate was 35% with a partial response in 4 patients and stable disease for 8 weeks or more in 14 patients. Temsirolimus has appeal as an agent in combination with radiation for NSCLC because it has established anti-proliferative and anti-angiogenic activity in multiple epithelial tumors and has non-overlapping toxicities with radiation. Inhibition of the mTOR pathway and the downstream HIF1-α has been shown to augment the cytotoxic effect of radiation *in vitro* and in xenograft studies.[16–18] However, there is scant clinical experience with temsirolimus in combination with radiation. The use of salvage temsirolimus along with involved field radiation in a single patient with refractory mantle cell lymphoma has been reported.[19] A phase I study investigated the combination of temsirolimus combined with temozolamide and radiation in patients with glioblastoma multiforme, which was associated with grade 4/5 infections in 3 of 12 patients.[20] The use of temsirolimus with thoracic radiotherapy for NSCLC has not been reported. We believe it is critical to test the safety and feasibility of

single agent temsirolimus in combination with thoracic radiation before adding this agent in the setting of concurrent chemoradiation in patients with potentially curable locally advanced NSCLC. We therefore conducted a phase I study to establish the safety of temsirolimus in combination with thoracic radiation alone in patients who were not candidates for curative therapy with concurrent chemoradiation.

Patients and methods

Patient Selection

Patients with histologically or cytologically confirmed non-small cell lung cancer with an indication for palliative thoracic radiation were enrolled. Patients who were candidates for definitive chemoradiation with curative intent were excluded. Patients were required to have radiographically measurable disease, ECOG performance status of 0–2 and adequate hematologic, hepatic and renal function (leukocytes ≥3000; ANC ≥1500 cells/mm3; platelets ≥ 100,000/mm3; total bilirubin <1.5; AST/ALT less than 2.5 times the upper limit of normal levels, normal creatinine or CrCl>60 mL/min. Prior systemic therapies were allowed long as treatment was completed at least 4 weeks prior to study entry and all treatment related toxicities had resolved. Women of child-bearing potential and men were required to agree to the use of adequate contraception prior to study entry and for the duration of the study participation.

Patients were excluded from this study if they had received prior treatment with temsirolimus, or had received prior radiation therapy directed at the tumor volume to be treated with radiotherapy on this protocol. In addition, patients who were receiving any other investigational agents, hepatic enzyme-inducing anticonvulsants, or other CYP3A4 inducers were excluded. Patients with symptomatic brain metastasis were not allowed on the study. Other exclusion criteria included known hypersensitivity reactions to macrolide antibiotics, uncontrolled intercurrent illness including, not limited to symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements; known HIV-positivity on combination antiretroviral therapy. Written informed consent was obtained from all patients, and the trial was approved by the Washington University Human Research Protection Office.

Dosage and administration

Temsirolimus was administered as a weekly 30-minute intravenous infusion, with the starting dose of 20 mg on day 1. The other dose levels used on this study are described in table 1. Temsirolimus was administered on a weekly basis for a total of four weeks. Radiotherapy began on day 2 and consisted of daily fractions of 2.5Gy, 5 days per week to a total cumulative dose of 35 Gy for a total of 14 days. Radiotherapy treatments were designed at the discretion of the radiation oncologist per protocol such that > 95% of the dose encompassed the planning target volume (PTV) while restricting the volume of lung receiving in excess of 20 Gy to < 40%, the entire heart volume to < 25 Gy, and spinal cord to < 50 Gy. Routine supportive care was permitted per institutional guidelines.

Study Design and Treatment Plan

The primary endpoint of the trial was maximum tolerated dose (MTD) of temsirolimus when given concurrently with thoracic radiation. Secondary endpoints included evaluation of safety of this regimen in patients with NSCLC, and determination of dose-limiting toxicities (DLT).

All toxicities were graded according to the NCI CTCAE v.3.0. DLT was defined as any grade 4 hematologic toxicity with the exception of anemia, any grade 4 non-hematologic toxicity related to study therapy, grade 3 or 4 pneumonitis or esophagitis, treatment delay of temsirolimus for more than 14 consecutive days due to study related toxicity, treatment delay of radiation therapy for more than 14 consecutive days because of study related toxicity, and death on study or within 30 days of receiving study therapy. The MTD was defined as the dose level which led to DLT in no more than one patient within the cohort.

A conventional 3+3 design was used to define MTD. However, a maximum of six patients were planned to be treated at the initial temsirolimus dose level 1 (20 mg) to ensure tolerability before dose escalation. If a DLT occurred in 0 or 1 patients, then the plan was to enter additional patients in the next higher dose cohort (dose level 2). However, if DLTs were observed in 2 or more patients enrolled in dose level 1, additional six patients would be enrolled in the next lower dose cohort (dose level-1). There was no intra-patient dose escalation. The patients were evaluated for a minimum of 90 days after initiation of temsirolimus, or recovery to grade 1 toxicities, whichever occurred later (excluding alopecia).

Follow-up studies

Toxicity assessments were performed weekly during the first five weeks and then every four weeks thereafter to evaluate for DLT. Physical exams were performed every two weeks during the first four weeks and then every four weeks thereafter. Radiologic evaluation was performed at baseline and at eight weeks after initiation of treatment. Response was defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria.

Results

Patient characteristics

Between March 2009 and February 2011, 10 patients were enrolled in this study (Figure 1 **and** Table 2), of which 5 were men and 5 were women. The median age of these patients was 62.5 years (range 46–83). Patients were treated on two dose levels: 4 patients received treatment on dose level 1 (temsirolimus 20 mg) and 6 received treatment on dose level -1 (temsirolimus 15 mg). Patients received a median of 3.5 doses of temsirolimus. Five patients received all 4 doses of temsirolimus. Eight patients completed their course of radiation therapy.

Toxicities

Four patients were enrolled at dose level 1. One patient registered to the protocol received two doses of temsirolimus and three doses of radiation and expired at home. This event was

considered a DLT per protocol, even though the event was attributed to the patient's lung cancer and not related to protocol therapy. Another patient treated at dose level 1 experienced grade 3 pneumonitis, grade 4 fatigue and grade 4 lymphopenia related to protocol therapy meeting the definition of DLT (table 3). This patient developed pneumonitis on day 10 of radiation, after receiving 2 doses of temsirolimus. This patient was able to complete radiation therapy to a total dose of 35 Gy, but did not receive any additional doses of temsirolimus. The V20 was 22% and the mean lung dose was 9.8 Gy. Since two patients had DLT, we de-escalated the dose of temsirolimus to dose level -1. Of the first three patients treated at dose level-1, one patient developed grade 3 pulmonary hemorrhage from a fungating right mainstem bronchus mass after receiving only 2 radiation fractions to a total dose of 5 Gy, and underwent bronchial artery embolization No other DLTs occurred at this dose level when three additional patients were enrolled. The MTD was determined to be dose level -1, which comprised of temsirolimus 15 mg intravenously weekly with concurrent radiotherapy.

Antitumor activity

Two patients were not evaluable for response. One patient was removed from study due to sudden death at home. She had received 1 dose of temsirolimus (dose level 1) and 3 days of radiation and her death was thought to be unrelated to the study treatment. A second patient was removed from study following 1 dose of temsirolimus and 2 days radiation due to hemoptysis. Eight patients were evaluable for anti-tumor activity. Two of the 8 evaluable patients had stable disease, 3 patients had a partial response, and 3 patients had progressive disease with new lesions outside the radiation treatment field.

Discussion

Non-small cell lung cancer is a molecularly diverse disease, and a driver mutation has been identified in 54% of patients[21] Despite the striking benefit seen with the use of agents such as erlotinib and crizotinib in molecularly selected patients with advanced stage NSCLC, empiric use of targeted agents has not improved the outcomes in patients with locally advanced NSCLC. The use of the vascular endothelial growth factor inhibitor, bevacizumab, with radiation has been associated with development of trachea-esophageal fistula.[9] Maintenance therapy with gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, following completion of chemoradiation in molecularly unselected NSCLC was associated with worse overall survival.[8] Induction chemotherapy followed by gefitinib and concurrent thoracic radiation in patients with unresectable adenocarcinoma, selected by light/never smoking status only, did not meet pre-defined criteria for feasibility.[22] In order to improve cure rates in locally advanced NSCLC, rationally selected, effective targeted therapies need to be identified that can be given safely with radiation therapy. Future studies of targeted agents with radiation need to be directed towards molecularly selected patient populations.

This is the first report to the best of our knowledge, of the use of temsirolimus along with thoracic radiation in patients with lung cancer. The outcomes for patients with locally advanced NSCLC treated with definitive chemoradiation have reached a plateau.[23] The

successful incorporation of targeted agents, such as inhibitors of mTOR in this setting requires better understanding molecular markers of response that can be used to select patients. Somatic mutations in tuberous sclerosis complex 1 (*TSC1*) gene and inactivation of neurofibromatosis type 2 gene (*NF2*) were recently identified as potential markers of response to mTOR therapy, through sequencing of the tumor genome of a single patient with metastatic bladder cancer, who achieved complete response of greater than 2 years duration to everolimus.[24] Inactivating somatic mutations of *STK11* (*LKB1*) reported in 34% of lung adenocarcinomas and 19% of squamous cell carcinomas could potentially identify patients likely to respond to temsirolimus given the sensitivity of a cell line with loss of *STK11* to rapamycin.[25–27] Mutations in *PIK3CA* have been shown to sensitize cancer cells to everolimus, but a concurrent mutation in *KRAS* or *BRAF* is predictive for resistance to mTOR inhibition.[28] Future studies of mTOR inhibitors in conjunction with thoracic radiation or chemoradiation should select patients based on these biomarkers. This strategy has already been employed in an ongoing phase II study of sunitinib or temsirolimus in patients with advanced rare tumors, in which patient selection is based on suspected or known germline mutations in *PTEN*, *TS1/2*, *LKB1* and *NF1 or 2* (NCT01396408).

Conclusions

The combination of temsirolimus 15mg weekly and thoracic radiation is well-tolerated and warrants further investigation, perhaps in a molecularly defined subset of patients.

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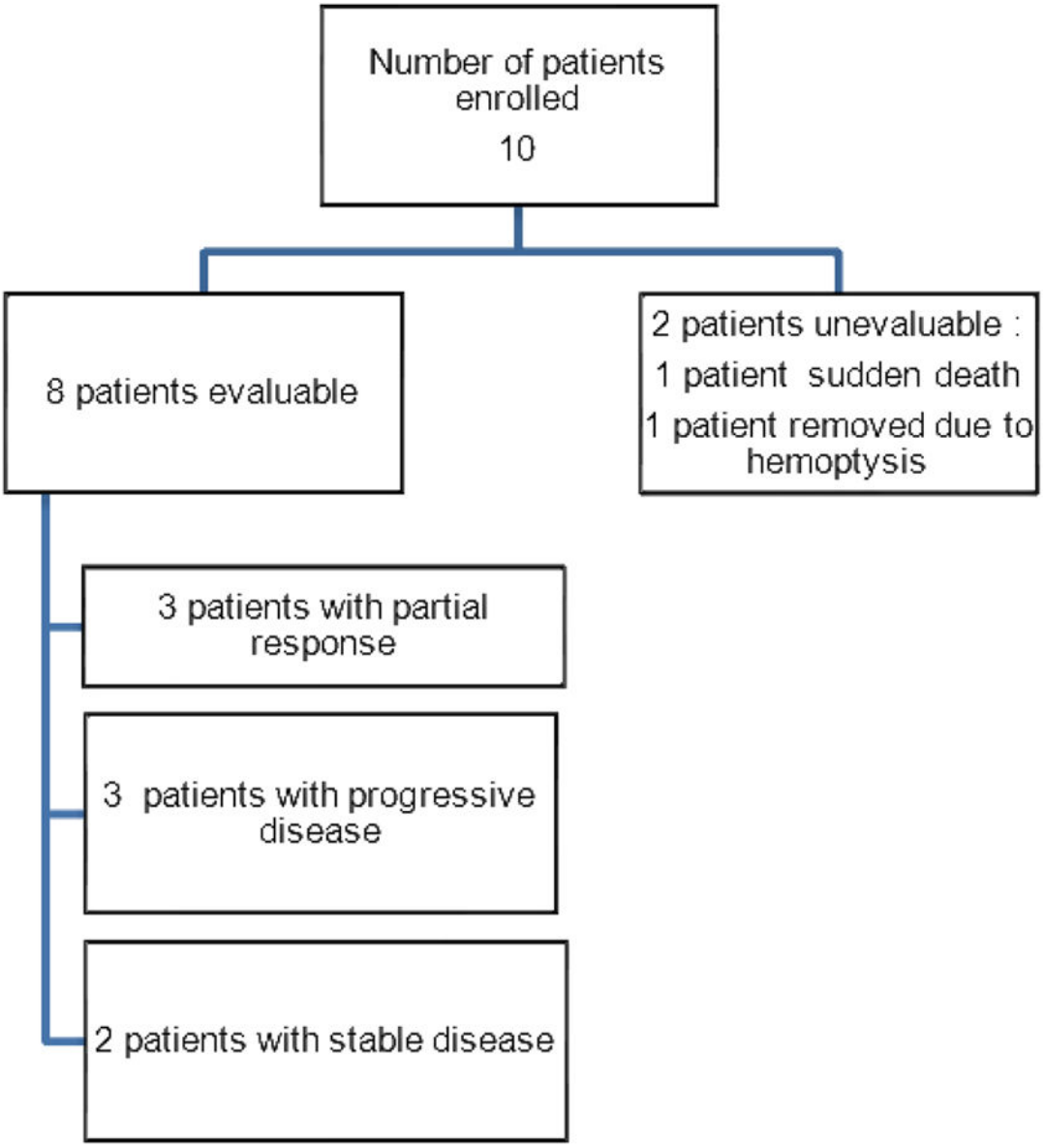

Figure 1.
Flow diagram of patients enrolled on study

Table 1

Dose escalation schema

Cohort	Temsirolimus weekly
−1	15 mg
1	20 mg
2	25 mg

Table 2

Patient characteristics

Characteristics	No. of patients
Age	
Median	62.5
Range	46–83
Sex	
Male	5
Female	5
ECOG Performance status	
0	1
1	9
Stage	
IV	9
Recurrent	1
Histology	
Adenocarcinoma	5
Squamous cell carcinoma	3
Poorly differentiated NSCLC	2
Prior radiotherapy	2
Head and neck radiation	1
Gamma knife for brain metastasis	1
Prior chemotherapy	6
Platinum doublet or triplet	6
Docetaxel	1
Pemetrexed	1
rlotinib	1

Table 3

Toxicity profile

Toxicity	Cohort (1) (N=4)			Cohort (−1) (N=6)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Cardiovascular	3			1		
Constitutional	3		1*^	3		
Gastrointestinal	2	1		5		
Lymphopenia	1		1*^	2	2	
Neutropenia				2		
Decreased platelet count	1			2		
Other hematological	1			2	1	
Infection	2				1	
Metabolic/Laboratory	3			3	2	
Pain		2		4		
Pulmonary	2	1*^		2	1*	
Neurologic	2			4		
Dermatologic	1			3		
Hemorrhage/ Thromboembolic		1		1	2	
Sudden Death	1*					

*Dose limiting toxicities

^This patient developed all of the following: grade 3 pneumonitis, grade 4 fatigue and grade 4 lymphopenia.