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RTOG 0913: A Phase I Study of Daily Everolimus (RAD001) In Combination with Radiation Therapy and Temozolomide in Patients with Newly Diagnosed Glioblastoma

Prakash Chinnaiyan, MD[1], **Minhee Won, MA**[2], **Patrick Y. Wen, MD**[3], **Amyn M. Rojiani, MD, PhD**[4], **Merideth Wendland, MD**[5], **Thomas A. Dipetrillo, MD**[6], **Benjamin W. Corn, MD**[7], and **Minesh P. Mehta, MD, FASTRO**

[1]Department of Radiation Oncology, Experimental Therapeutics and Cancer Imaging and Metabolism, H. Lee Moffitt Cancer Center, Tampa, FL

[2]Radiation Therapy Oncology Group, Philadelphia, PA

[3]Center for Neuro-Oncology, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA

[4]Department of Pathology, Medical College of Georgia, Augusta, GA

[5]Radiation Oncology, USON-Williamette Valley Cancer Center, Eugene, OR

[6]Department of Radiation Oncology, Rhode Island Hospital, Providence, RI

[7]Department of Radiation Oncology, Tel-Aviv Medical Center, Tel-Aviv, Israel

[8]Department of Radiation Oncology, University of Maryland, Baltimore, MD

Abstract

Purpose—To determine the safety of the mTOR inhibitor everolimus (RAD001) administered daily with concurrent radiation and temozolomide in newly diagnosed glioblastoma patients.

Methods and Materials—Everolimus was administered daily with concurrent radiation (60 Gy in 30 fractions) and temozolomide (75 mg/m2/day). Everolimus was escalated from 2.5 (Dose Level 1), to 5 (Dose Level 2), to 10 mg/day (Dose Level 3). Adjuvant temozolomide was delivered at 150-200 mg/m2 on days 1 to 5 every 28 days for up to 12 cycles with concurrent everolimus at the previously established daily dose of 10 mg/day. Dose escalation continued if a dose level produced DLTs in ≤ 2 of the first 6 evaluable patients.

Results—Between October 28, 2010 and July 2, 2012, the Radiation Therapy Oncology Group (RTOG) 0913 protocol initially registered a total of 35 patients, with 25 patients successfully meeting enrollment criteria receiving drug and evaluable for toxicity. Everolimus was successfully escalated to the predetermined MTD of 10 mg/day. Two of the first 6 eligible patients experienced

Corresponding Author: Prakash Chinnaiyan, MD, Assistant Member, Department of Radiation Oncology and Experimental Therapeutics, H. Lee Moffitt Cancer Center and Research Institute, SRB3, 12902 Magnolia Drive, Tampa, FL 33612, Office: 813.745.3425, Fax: 813.745.3829, prakash.chinnaiyan@moffitt.org.

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a DLT at each dose level. DLTs included: gait disturbance, febrile neutropenia, rash, fatigue, thrombocytopenia, hypoxia, ear pain, headache, and mucositis. Other common toxicities were Grade 1/2 hypercholesterolemia and hypertriglyceridemia. At the time of analysis, there was one death reported, which was attributed to tumor progression.

Conclusions—Daily oral everolimus (10 mg) combined with both concurrent radiation and temozolomide followed by adjuvant temozolomide, is well tolerated, with an acceptable toxicity profile. A phase II randomized clinical trial with mandatory correlative biomarker analysis is currently underway, designed to both determine the efficacy of this regimen and identify molecular determinants of response.

Introduction

Glioblastoma is the most common and aggressive adult brain tumor. Although clinical improvements have recently been attained with the addition of temozolomide to radiation, long-term prognosis remains poor (1, 2). The recent characterization of glioblastoma by The Cancer Genome Atlas (TCGA) has revealed several molecular aberrations and copy-number changes, defining 3-4 broad categories of molecular profiles within this heterogeneous entity (3), suggesting the possibility of utilizing targeted agents, at least for subsets of glioblastoma patients. Therefore, identifying novel agents that target specific pathways contributing towards glioblastoma growth and resistance, and combining them with the current therapeutic platform of radiation and temozolomide, remains an active area of investigation. Recent investigations have demonstrated the capacity of mammalian target of rapamcyin (mTOR) to serve as a regulatory hub for several key prosurvival pathways associated with glioblastoma growth (4, 5). These specific pathways have also been associated with radiation resistance, with preclinical studies suggesting that targeting mTOR represents a rational approach for enhancing radiation response (6-9). In addition, mTOR influences tumor angiogenesis, a pathological hallmark of this tumor (10). Therefore, by influencing tumor growth, therapeutic resistance, and tumor microenvironment, the mTOR signaling axis represents an attractive therapeutic target in glioblastoma.

Everolimus (RAD001), a derivative of rapamycin, is an oral inhibitor of mTOR that has demonstrated anti-tumor activity and has recently been approved by the FDA for several tumor types, including renal cell (11) and breast cancer (12), pancreatic neuroendocrine tumors (13), and subependymal giant-cell astrocytomas associated with tuberous sclerosis (14). The current study reports the RTOG phase I experience determining the safety of integrating everolimus with radiation and temozolomide in patients with newly diagnosed glioblastoma. Daily dosing of everolimus with adjuvant temozolomide has recently been established (15). With preclinical studies suggesting mTOR inhibition may serve as a promising approach for radiation sensitization, the goal of this study was to determine the recommended Phase II dose of everolimus when administered daily with concurrent radiation therapy and temozolomide in newly diagnosed glioblastoma.

Methods and Materials

Selection criteria

Eligibility criteria were as follows: 18 years of age or older; Karnofsky performance status >= 70; centrally reviewed newly diagnosed, unifocal, supratentorial glioblastoma; no prior chemotherapy, treatment with an mTOR inhibitor, or radiation to the head or neck area (except T1 glottic tumors); standard hematologic and metabolic panel within normal limits (absolute neutrophil count ≥ 1800 cells/mm^3, platelets ≥ 100,000 cells/m^3, hemoglobin ≥ 10 g/dl, PT/INR ≤ 1.5, BUN ≤ 30 mg/dl, creatinine ≤ 1.5 × normal range, bilirubin ≤ 1.5 × normal range, and ALT/AST ≤ 2.5 normal range); fasting cholesterol ≤ 300 mg/dL or ≤ 7.75

mmol/L; triglycerides ≤ 2.5 × the upper limit of normal; no concurrent use of enzyme-inducing anti-epileptic drugs (EIAEDs); no severe active co-morbidity; no history of deep vein thrombosis or pulmonary embolism; no malignancy (within 3 years) except nonmelanomatous skin cancer or carcinoma in situ of the cervix or bladder; no pregnancy or lactation; radiation must have been initiated within 5 weeks after surgery.

Treatment

Radiation Therapy Oncology Group (RTOG) 0913 is an ongoing phase I/IIR study combining daily everolimus with concurrent radiation and temozolomide; the phase I component has been completed. Radiation is delivered using intensity modulated radiation therapy (IMRT) or 3-dimensional (3D)-conformal radiation (60 Gy in 30 fractions of 2 Gy each). An initial target representing the T2/Axial FLAIR volume plus a tailored 2 cm margin was treated to 46 Gy in 23 fractions of 2 Gy each, followed by a 14 Gy boost (in 7 fractions of 2 Gy each) to the contrast enhancing tumor plus 2 cm margin. During radiation, temozolomide was delivered at 75 mg/m^2. To determine the maximum tolerated dose (MTD) of everolimus when administered concurrently with daily temozolomide and radiation, everolimus was escalated from 2.5 mg/day (Dose Level 1), to 5 mg/day (Dose Level 2), to 10 mg/day (Dose Level 3). As the pharmacokinetics of everolimus has been studied extensively in previous investigations, they were not performed in this trial. Prophylaxis against pneumocystis jiroveci pneumonitis/pneumocystis carinii pneumonitis (PJP/PCP) was strongly encouraged. Adjuvant temozolomide was delivered at 150-200 mg/m2 on days 1 to 5 every 28 days for up to 12 cycles with concurrent daily everolimus at the previously established daily dose of 10 mg/day (15).

Patient evaluation

Patients were evaluated for both hematologic and nonhematologic adverse events weekly during the course of radiation therapy and the two weeks following the completion of radiation. Treatment response and adverse events were then monitored every other month, beginning 4 weeks following the completion of radiation therapy, with MR imaging.

Statistical methodology

Toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4. DLT was defined as any of the following events occurring during the first 8 weeks of treatment with everolimus and concurrent radiation/temozolomide: grade 3 or 4 thrombocytopenia, grade 4 anemia; grade 4 neutropenia lasting more than 7 days; febrile neutropenia, any non-hematologic grade 3 or greater toxicity (excluding alopecia) despite maximal medical therapy; grade 4 radiation-induced skin changes; any episode of non-infectious pneumonitis.

Dose escalation continued (or MTD was defined if at the final dose level) if no patient of the first 3 eligible experienced a dose limiting toxicity (DLT) or the everolimus dose produced DLTs in ≤ 2 out of the first 6 eligible patients. The DLT rate chosen was slightly higher than the more conventional < 2/6 patients due to the relatively high frequency of expected toxicities during treatment with radiation therapy and temozolomide.

Results

Patient Characteristics

Between October 28, 2010 and July 2, 2012, a total of 35 patients were initially registered to this study (Dose Level 1: 11 patients, Dose Level 2: 13 patients, Dose Level 3: 11 patients). A total of 26 patients went on to receive drug (Dose Level 1: 8 patients, Dose Level 2: 10 patients, Dose Level 3: 8 patients). Reasons for trial exclusion included checklist failure

(n=5), progressive symptoms (n=2), inability to submit tissue for central review (n=1), and patient refusal (n=1). Of these patients, 25 were evaluable for toxicity; one case enrolled in Dose Level 2 was excluded from analysis due to previous history of DVT. The patient characteristics are shown in Table 1.

Toxicities

Dose-limiting toxicities were defined during concurrent treatment with everolimus, radiation, and temozolomide. Two of 8 patients experienced at DLT in Dose Level 1, described as gait disturbance and febrile neutropenia, both occurring after 5 weeks of treatment. Three of 9 patients experienced at DLT in Dose Level 2, including one patient with a papulopustular rash beginning after 5 weeks of therapy that continued for over 1 month despite medical management, one patient with fatigue and thrombocytopenia, and the last patient with hypoxia that began days after the initiation of therapy (only two of the first 6 patients experienced a DLT, so the dose was escalated to next level). Two of 8 patients experienced at DLT in Dose Level 3. Toxicities included ear pain, headache, and mucositis (occurring in both patients) that began within 2 weeks of therapy. A summary of Grade ≥ 3 toxicities are provided in Table 2 and a comprehensive list of all toxicities reported are included as Supplemental Table 1. An expected high incidence of Grade 1/2 hypercholesterolemia (n=15) and hypertriglyceridemia (n=16) was observed, and lymphocytopenia was the most common Grade 3/4 toxicity (n=15). At the time of analysis, there was one death reported, which was over 7 months following initiation of therapy (Dose Level 1) that was attributed to tumor progression. Daily everolimus with adjuvant temozolomide continued to be relatively well tolerated, with lymphocytopenia continuing to be a common adverse event. A list of all toxicities reported during the adjuvant phase is included as Supplemental Table 2.

Discussion

In this Phase I study, daily oral everolimus combined with both concurrent radiation and temozolomide was relatively well tolerated, with an acceptable rate of toxicity. Everolimus was successfully escalated to the predefined dose of 10 mg/day, which represents the dosing schedule demonstrating clinical benefit in two recent randomized Phase III trials in renal and breast cancer patients (11, 12). A similar study has recently been published by the North Central Cancer Treatment Group (NCCTG) demonstrating the safety of weekly everolimus (70 mg/week) with concurrent radiation and temozolomide in newly diagnosed glioblastoma patients (16). However, the clinical activity of everolimus was noted with daily dosing in two large Phase III clinical trials (11, 12) and preclinical and clinical pharmacokinetic (PK) and pharmacodynamics (PD) data suggest the optimal biologic activity of everolimus is with daily administration (17, 18). Specifically, Tanaka et al presented data based on a PK/PD model of S6 kinase 1 (S6K1) inhibition, which represents a putative biomarker of mTOR signaling, predicting daily dosing to have a more sustained effect on target inhibition despite similar total exposure (19). Therefore, we conducted this study to determine the safety of everolimus daily dosing.

One of the initial applications for mTOR inhibitors involved their role as an effective immunosuppressive therapy in transplant patients (20). Therefore, the potential of these agents increasing the risk of infection is a clear concern when used in cancer therapy, as demonstrated by a recent study testing a different mTOR inhibitor temsirolimus (CCI-779) in newly diagnosed glioblastoma (21). This risk did not seem to be increased with everolimus in both our study, which tested daily dosing, as well as the study performed by the NCCTG testing weekly dosing in glioblastoma patients (16), although this difference may be attributed to mandating PJP/PCP prophylaxis in the NCCTG study and strongly encouraging prophylaxis in our study. Interestingly, however, the NCCTG study did report

two cases of reactivation of hepatitis B, which led to the exclusion of patients with positive antigen or antibody from subsequent phase II evaluation. Therefore, continued evaluation of toxicities in patients being treated on this regimen is warranted.

Conclusion

Daily oral everolimus (10 mg) combined with both concurrent radiation and temozolomide and adjuvant temozolomide, is relatively well tolerated with an acceptable toxicity profile. A RTOG Phase II randomized clinical trial is currently underway designed to both determine the efficacy of this regimen and identify molecular determinants of response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Despite recent progress, overall outcomes in patients with glioblastoma remain poor. We performed a Phase I study combining the mTOR inhibitor everolimus with standard therapy in an effort to improve clinical outcomes in patients with newly diagnosed GBM. We found that daily everolimus combined with radiation and temozolomide is well tolerated with an acceptable toxicity profile. A phase II randomized clinical trial with is currently underway, designed to determine the efficacy of this regimen.

Table 1

Patient Characteristics

	Dose Level 1 (n=8)	Dose Level 2 (n=9)	Dose Level 3 (n=8)
Age (years)			
Median	58	57	57
Min - Max	39 - 72	39 - 69	31 – 73
Q1 - Q3	51.5 - 68.5	52 - 63	51.5 – 67
Gender			
Male	4 (50.0%)	8 (88.9%)	2 (25.0%)
Female	4 (50.0%)	1 (11.1%)	6 (75.0%)
Race			
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	1 (12.5%)
White	8 (100.0%)	9 (100.0%)	7 (87.5%)
Ethnicity			
Hispanic or Latino	0 (0.0%)	0 (0.0%)	1 (12.5%)
Not Hispanic or Latino	7 (87.5%)	8 (88.9%)	7 (87.5%)
Unknown (Individuals not reporting ethnicity)	1 (12.5%)	1 (11.1%)	0 (0.0%)
KPS			
70-80	3 (37.5%)	4 (44.4%)	3 (37.5%)
90-100	5 (62.5%)	5 (55.6%)	5 (62.5%)
Surgery			
Subtotal	2 (25.0%)	3 (33.3%)	4 (50.0%)
Total (gross)	6 (75.0%)	5 (55.6%)	4 (50.0%)
Other	0 (0.0%)	1 (11.1%)	0 (0.0%)
Neurologic Function			
No symptoms	2 (25.0%)	3 (33.3%)	3 (37.5%)
Minor symptoms	6 (75.0%)	5 (55.6%)	5 (62.5%)
Moderate symptoms	0 (0.0%)	1 (11.1%)	0 (0.0%)
RPA Class			
III	2 (25.0%)	1 (11.1%)	1 (12.5%)
IV	6 (75.0%)	7 (77.8%)	7 (87.5%)
V	0 (0.0%)	1 (11.1%)	0 (0.0%)

Q1 = first quartile; Q3 = third quartile.

RPA = Recursive Partitioning Analysis.

Table 2

Drug related adverse events (Grade ≥ 3)

	Dose Level 1 (n=8)			Dose Level 2 (n=9)			Dose Level 1 (n=8)		
	Grade			Grade			Grade		
	3	4	5	3	4	5	3	4	5
Anemia	1	0	0	0	0	0	0	0	0
Febrile neutropenia	1	0	0	0	0	0	0	0	0
CD4 count decrease	0	0	0	1	0	0	1	0	0
Lymphocytopenia	3	3	0	4	0	0	5	0	0
Neutropenia	0	1	0	0	0	0	0	0	0
Thrombocytopenia	0	1	0	0	1	0	0	0	0
Ear pain	0	0	0	0	0	0	1	0	0
Oral mucositis	0	0	0	0	0	0	1	0	0
Fatigue	1	0	0	1	0	0	0	0	0
Gait disturbance	1	0	0	0	0	0	0	0	0
Rash	0	0	0	1	0	0	0	0	0
Respiratory infection	0	0	0	1	0	0	0	0	0
Hyperglycemia	0	0	0	1	0	0	0	0	0
Hyponatremia	0	0	0	1	0	0	0	0	0
Muscle weakness	1	0	0	0	0	0	0	0	0
Headache	1	0	0	0	0	0	1	0	0
Insomnia	0	0	0	1	0	0	0	0	0
Hypoxia	0	0	0	1	0	0	0	0	0