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Phase II trial of an AKT inhibitor (perifosine) for recurrent glioblastoma

Thomas J. Kaley[1,5,*], **Katherine S. Panageas**[2,5], **Ingo K. Mellinghoff**[1,5], **Craig Nolan**[1,5], **Igor T. Gavrilovic**[1,5], **Lisa M. DeAngelis**[1,5], **Lauren E. Abrey**[1,5,6], **Eric C. Holland**[3,4,5,7], **Andrew B. Lassman**[1,5,8,*]

[1]Departments of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA. [2]Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA. [3]Neurosurgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA. [4]Cancer Biology and Genetics, Memorial Sloan Kettering Cancer Center, New York, NY, USA. [5]Brain Tumor Center, Memorial Sloan Kettering Cancer Center, New York, NY, USA. [6]Current affiliations: Novartis Oncology, Basel, Switzerland [7]Human Biology, and Solid Tumor and Translational Research, Fred Hutchinson Cancer Research Center, Alvord Brain Tumor Center, University of Washington, Seattle, WA, USA [8]Department of Neurology & Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY, USA

Abstract

Purpose: Perifosine (PRF) is an oral alkylphospholipid with antineoplastic effects and reasonable tolerability. It inhibits signaling through the PI3/AKT axis and other cascades of biologic importance in glioblastoma, and has promising pre-clinical activity in vitro and in vivo. Therefore, we conducted a phase II open-label single-arm clinical trial of perifosine for patients with recurrent glioblastoma (GBM).

Methods: We planned to accrue up to 30 adults with recurrent GBM with a minimum Karnofsky Performance Status of 50 following radiotherapy but without other restrictions on the number or types of prior therapy. Concurrent p450 stimulating hepatic enzyme inducing anticonvulsants were

[*]Co-corresponding Authors: Thomas J. Kaley, Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, New York, USA, Tel 212-639-512, Fax 212-717-3519, kaleyt@mskcc.org. Andrew B. Lassman, MD; Department of Neurology and Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, 710 West 168th Street, New York, New York, USA, Tel 212-342-0871, Fax 212-342-1246, ABL7@cumc.columbia.edu.

CONFLICT OF INTEREST

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prohibited. Patients were treated with a loading dose of 600mg PRF (in 4 divided doses on day 1) followed by 100mg daily until either disease progression or intolerable toxicity. The primary endpoint was the 6-month progression free survival (PFS6) rate, with at least 20% considered promising. Accrual was continuous but if 0 of the first 12 patients with GBM reached PFS6, then further accrual would terminate for futility. Patients with other high grade gliomas were accrued concurrently to an exploratory cohort.

Results: Treatment was generally well tolerated; gastrointestinal toxicities were the most common side effects, although none resulted in treatment discontinuation. However, there was limited to no efficacy in GBM (n=16): the PFS6 rate was 0%, median PFS was 1.58 months [95%CI: (1.08, 1.84)], median overall survival was 3.68 months [95%CI: (2.50, 7.79)], with no radiographic responses. There was a confirmed partial response in one patient with anaplastic astrocytoma (n=14).

Conclusions: PRF is tolerable but ineffective as monotherapy for GBM. Preclinical data suggests synergistic effects of PRF in combination with other approaches, and further study is ongoing.

Keywords

Glioblastoma; phase II; perifosine; AKT; chemotherapy; clinical trial

INTRODUCTION:

Despite aggressive therapy, glioblastoma (GBM) remains an incurable neoplasm. Median overall survival (OS) is approximately 1–2 years from diagnosis.[1] At recurrence, most agents are of limited efficacy and median progression-free survival (PFS) is 2–3 months with a 6-month progression-free survival (PFS6) rate under 15%.[2–4] Although bevacizumab is associated with a PFS6 rate of 30–50% that is higher than reported with cytotoxic agents, it does not appear to improve OS.[5] Clearly, better treatments are needed.

Alkylphospholipids are novel agents with different toxicities and mechanisms of action than traditional chemotherapies.[6] Miltefosine is a naturally occurring compound with a broad spectrum of antineoplastic mechanisms and is effective against cutaneous breast cancer metastases when applied topically, but profound gastrointestinal toxicities limit its practical use for prolonged systemic delivery.[7] Therefore, other in-class agents with improved tolerability were developed, leading to the discovery of perifosine (PRF)[7] which inhibits several signal transduction pathways of importance in human cancers, especially PI3K/AKT[7][8] Early trials demonstrated reasonable tolerability with mainly gastrointestinal toxicities.[9] The half-life exceeds 100 hours, and early studies in systemic malignancies led to standardization of an initial load to achieve steady state in serum rapidly, followed by prolonged administration of a lower (15%−20% of the load) dose daily thereafter,[10] with anecdotal responses in various cancers.[11][12]

Mouse gliomas that model the human disease molecularly and histologically have been developed using retroviral injection of oncogenes of interest in transgenics susceptible to infection in glia or glial progenitors, as reviewed elsewhere.[13] Such models provide a tool

to test novel therapeutic agents pre-clinically. For example, forced activation of the AKT and RAS signal transduction cascades is sufficient to induce GBMs in such mice.[14] Pre-clinical data with genetically engineered mouse gliomas[13] demonstrated that PRF reduces AKT phosphorylation as well as that of the RAS effector ERK,[15] and induced tumor necrosis in vivo.[16] As the PI3K/AKT and RAS/MEK/ERK signal transduction cascades are overly activated in the vast majority of human GBMs,[17] we conducted a clinical trial of perifosine to explore efficacy in patients with recurrent GBMs (NCT00590954).

PATIENTS AND METHODS:

This was a prospective, single-center, open-label single arm phase II trial that accrued at Memorial Sloan Kettering Cancer Center.

Eligibility

Patients were required to have histologically proven GBM with unequivocal evidence of tumor progression on neuroimaging. Prior radiotherapy was required but there was otherwise no limit on the number of recurrences or prior therapies. Adults with Karnofsky Performance Status ≥50 (to broaden eligibility and accrue as quickly as possible) who had recovered from any prior drug therapy (including bevacizumab) delivered ≥ 4 weeks were eligible if they had normal end-organ function at baseline (marrow, liver, renal). Concurrent hepatic p450 enzyme-inducing anticonvulsants were prohibited both for ≥2 weeks before treatment with and during PRF because of potential effects on drug pharmacokinetics as is typical in GBM trials of novel agents.

Treatment Plan

Patients received 600mg PRF as a loading dose (in 4 divided doses of 150mg each) on day 1 of cycle 1 followed by 100mg daily continuously as a previously established recommended phase II schedule in other cancers. A cycle was defined as 28 days although treatment was intended to be continuous until either disease progression or intolerable toxicity. Monitoring by complete blood counts and serum chemistries were performed at baseline, after 1 week, and before each additional cycle of therapy. Patients were assessed for response with contrast-enhanced brain MRI scans and clinical examinations at baseline and then on alternate cycles using Macdonald criteria.[18] In addition, Response Assessment in Neuro-Oncology (RANO) criteria,[19] published after the trial was designed, were also applied post-hoc. Treatment-related toxicities were evaluated utilizing the National Cancer Institute Common Terminology Criteria Adverse Event (CTCAE) version 3.0, and dose reductions by 50mg daily were allowed for grade ≥ 3 toxicities or unacceptable grade 2 toxicities at least possibly attributed to PRF.

The study was approved by the appropriate local institutional review board; all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Statistical Considerations

This study was designed as a single-arm, open label, Simon two-stage phase 2 trial [20] with plans treat a maximum of 37 patients with recurrent GBM. The primary endpoint was the PFS6 rate with PFS defined as the time from starting treatment until progression of disease or death from any cause. A PFS6 rate of 5% was considered not promising, PFS6 of 20% worthy of further study, and the probabilities of type I and II error (falsely accepting a non-promising therapy and falsely rejecting a promising therapy, respectively) set at 10% each, In addition, to reduce the number of patients required, if 0 of the first 12 patients (first stage) reached PFS6, then accrual would terminate for futility, although accrual of additional patients was permitted while follow-up of the first 12 treated was ongoing. At the end of the second stage, if ≤ 3 patients were progression-free at 6 months then the trial would be declared negative Secondary endpoints included radiographic response rate, median PFS, median overall survival (from treatment start until death from any cause), and toxicity. Time to event endpoints were evaluated utilizing Kaplan-Meier methodology and calculated from the start of treatment.

In an exploratory cohort, patients with other high-grade gliomas (such as anaplastic astrocytomas, oligodendrogliomas) were accrued with outcomes to be reported descriptively and without pre-planned efficacy goals.

As AKT inhibition by PRF could alter glucose metabolism, we explored brain ^{8}Fluorodeoxyglucose-positron emission tomography (FDG-PET) as pharmacodynamic surrogate effect and potential predictor of response. Therefore, we performed brain FDG-PET imaging at baseline and during cycle 1 in willing patients.

RESULTS

Patient Characteristics

There were 16 patients with GBM (8 men, 8 women) with a median age of 48 years (range 23–77), including 4 accrued while the first 12 were followed for PFS6 (table 1). One additional patient with GBM withdrew consent prior to any study intervention and was not included in any of the analyses. All treated patients with GBM had been previously undergone radiotherapy and received temozolomide, and 8 (50%) were previously treated with bevacizumab. Patients were heavily pretreated with a median number of 5 prior therapies (range 3–10). In addition, 14 patients (6 women, 8 men; median age 52 years, range 33–74) with anaplastic gliomas (9 oligodendroglioma, 5 astrocytoma) were accrued.

Response and Outcome

All 16 treated patients with GBM are included in the time-to-event and response analyses, and all have died; thus, the data is fully mature. None of the first 12 patients with GBM reached PFS6, and further accrual was terminated accordingly. Among the 4 patients remaining on study at that time, one withdrew consent, and the other 3 had imaging performed which confirmed disease progression. Among all 16 patients, none (0%) reached PFS6, median PFS was 1.58 months [95% CI: (1.08, 1.84)], and median overall survival was 3.68 months [95% CI: (2.50, 7.79)]. There were no radiographic responses; best response

(both Macdonald and RANO) was stable disease in 2, progressive disease in 12, and 2 were not evaluable because of withdrawal from the study (2) before response assessment.

Among 14 with anaplastic gliomas accrued to the exploratory cohort, PFS6 rate was 14%, median PFS was 2.12 months [95%CI: (1.84, 12.79)], and median overall survival was 9.69 months [95%CI: (5.29, NA)]. Post-hoc central review by the principal investigators (TJK, ABL) demonstrated that best response (Macdonald and RANO) was partial in 1 (anaplastic astrocytoma), stable disease in 4, progressive disease 7, and not evaluable in 2. Of note, one with anaplastic oligodendroglioma had reduced cross-sectional area of contrast enhancement of >50%, but died of disease before a confirmatory MRI was obtained and scored as stable disease; one with anaplastic astrocytoma had a minor response (reduction in contrast-enhancing tumor size of <50% confirmed on multiple subsequent MRIs) but was included among those scored as stable disease.

Toxicity

Among all 30 patients (16 GBM, 14 anaplastic gliomas), no grade 4 (or 5) PRF-attributed toxicities were observed. Grade 3 toxicities (table 2) were uncommon and included hyperglycemia (n=4), hypophosphatemia (n=2), lymphopenia (n=2), neutropenia (n=1), and increased alanine aminotransferase (ALT, n=1). One patient required dose reduction for persistent grade 2 hypophosphatemia, but none discontinued PRF because of toxicity. Common grade 1–2 toxicities included thrombocytopenia, hyperglycemia, hypophosphatemia, transaminitis, and gastrointestinal complaints (nausea, vomiting, diarrhea, and anorexia; Table 2) as previously reported for PRF.

FDG-PET Imaging

There were too few scans to make any formal statistical analyses, resulting in part from the optional nature of the imaging. Descriptively, there were no obvious changes in tumor glucose uptake during treatment, nor any obvious correlation between uptake on baseline FDG-PET and response by subsequent MRI. This may be confounded by the lack of clinical efficacy observed with PRF in the trial.

DISCUSSION

PRF as a single agent is not active in recurrent GBM. However, it was reasonably well tolerated, and radiographic improvements were observed in 3/14 patients with other high-grade gliomas including one confirmed partial response. Potential reasons for treatment failure include existence of redundant pathways in the AKT signaling axis such that monotherapy with PRF is insufficient for response. It is also possible that the tumors in this heavily pretreated patient population studied (prior therapy, low KPS) were also particularly aggressive and treatment refractory. Molecular correlations with outcome were not pursued because of the lack of efficacy.

While this trial was ongoing and following completion of accrual, further pre-clinical studies were conducted combining PRF with other therapies.[15,16] Results suggested that PRF combined with the mTOR inhibitor temsirolimus shut down signaling through the PI3K/AKT/mTOR axis more effectively than either PRF or temsirolimus alone and

synergistically induced massive intra-tumoral cell death in tumor-bearing mice.[16] Therefore, we subsequently conducted a phase I trial of dual-drug therapy combining PRF with temsirolimus,[21] as well as planned other possible combinations pending outcome of the drug studies and further evolution of the preclinical science.

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Table 1:

Patient Characteristics

	Glioblastoma (n=16)	**Anaplastic Glioma (n=14)**
Gender		
Men	8 (50%)	8 (38%)
Women	8 (50%)	6 (62%)
Median age (range)	48 (23–77)	52 (33–74)
Median Karnofsky Performance Status (range)	80 (50–90)	90 (60–100)
Prior radiotherapy	16 (100%)	14 (100%)
Prior chemotherapy	16 (100%)	14 (100%)
Prior bevacizumab	8 (50%)	0 (0%)
Median number of prior therapies	5 (3–10)	5 (3–10)

Table 2:

Grade 3 toxicities

Toxicity	N	%
Hyperglycemia	4	13
Hypophosphatemia	2	7
Lymphopenia	2	7
Neutropenia	1	3
Increased alanine aminotransferase	1	3

Adverse events possibly, probably, or definitely attributed to perifosine, per patient (n=30)

Table 3:

Grade 1 and 2 toxicities

Toxicity	N	%
Elevated alanine aminotransferase (ALT)	12	40
Hyperglycemia	12	40
Fatigue	10	33
Thrombocytopenia	9	30
Diarrhea	7	23
Elevated aspartate transaminase (AST)	6	20
Hypophosphatemia	5	17
Leukopenia	5	17
Nausea	5	17
Alkaline Phosphatase	3	10
Hyperkalemia	2	7
Vomiting	2	7
Dysgeusia	1	3
Hypernatremia	1	3
Hypertriglyceridemia	1	3
Lymphopenia	1	3

Adverse events possibly, probably, or definitely attributed to perifosine, per patient (n=30)