Phase I Clinical Trial of Intratumoral Reovirus Infusion for the Treatment of Recurrent Malignant Gliomas in Adults

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Abstract

Introduction
Reovirus is an RNA virus shown to have in vivo activity in malignant glioma (MG) in preclinical studies. The goal of this multicenter Phase I study was to determine the DLT and maximum tolerated dose, as well as the effects of intratumoral reovirus infusion in patients with recurrent MG. The response rate of the targeted lesions was evaluated as a secondary endpoint.

Methods
Patients were adults with a first, second, or third recurrence of a histologically confirmed supratentorial MG with a Karnofsky Performance score of =60, and who had undergone prior surgery and radiation. A total of 15 patients were enrolled in a classic 3x3 dose escalation scheme with three patients treated at each of the following tissue culture infectious dose 50 doses: 1 x 10^8, 3 x 10^8, 1 x 10^9, 3 x 10^9, and 1 x 10^10. Each patient received a 72-hour infusion via one to four catheters implanted intraoperatively at the enhancing border of target lesions. Patients underwent examinations as well as MRI scans at baseline, time of discharge from infusion, and at 4, 8, 12, 16, and 24 weeks post infusion.

Results
There was one grade III adverse event (convulsions), felt to be possibly related to treatment, but no grade IV AEs probably or definitely related to treatment. Twelve patients had tumor progression, two had stable disease, and one had a partial response. Median survival was 140 days (range, 97 – 989), and one patient was still alive more than 16 months post treatment. Median time to progression was 61 days (range, 29 – 150 days). DLTs were not identified and a MTD was not reached.

Conclusions
A 72-hour intratumoral infusion of reovirus was well tolerated at the above doses in patients with recurrent MG.

Background

Oncolytic Viral Therapy
- Use of viruses that maintain their replicative life cycle in tumor cells and produce tumor cell death
- Resurgence in 1990's

Reovirus
- Respiratory Enteric Orphan Virus
- RNA virus
- Advantages:
- No genetic engineering required
- Not known to cause encephalitis
- Smaller than HSV
- Potentially replicates to higher titers

Convection Enhanced Delivery
- Continuous infusion of agent to area of interest via pressure rather than diffusion gradient
- Advantages: overcome limitations of access to CNS such as blood-brain barrier
- Limitations: tumor size, proximity to low-pressure sinks (pial surface, ventricles, tumor bed)
- Theory: replicating agents are better targets to overcome these limitations vs. static agents
- Proof of true convection with Reovirus not yet established

Goals of Phase I Infusion Trial

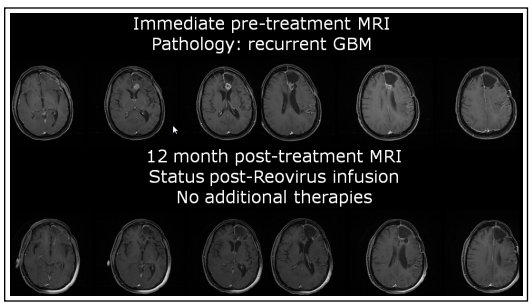
- Determine DLT and MTD of reovirus infusion
- Anti-tumoral effect of reovirus infusion
- Response rate of targeted lesions

- 1st study to utilize a continuous infusion rather than a single inoculation of reovirus

Study Design

- Sponsored by Oncolytics
- UAB, OSU and Cedars-Sinai
- Patients underwent stereotactic biopsy, then catheter implantation
- Patients received 400 microliters total dose per hour, 9.6 mL/day for total of 72 hour infusion divinded between 1-4 catheters implanted in the enhancing rim of tumor bed
- Dose escalation 3 x 3 design
- Initial dose level 1 x 10^8 TCID50
- Increased by 0.5 log increments
- Highest cohort at 1 x 10^10 TCID50
- Evaluated: Baseline, discharge, 4, 8, 12, 16, 24 weeks with exams and imaging

Results



Patient Demographics
Patients
- Enrolled: 18
- Treated: 15

KPS (median)
- Accrual: 90 (60-100)
- Day 28: 80 (70-90)

Age: 51.52 (26.22-76.3)
Race
- Caucasian: 14 (93.3%)
- Black: 1 (6.7%)

Sex
- Male: 10 (66.7%)
- Female: 5 (33.3%)

Significant Adverse Events

Adverse Events	Grade	Relationship to Viral Injection				
		Unrelated	Unlikely	Possibly	Probably	Definitely
Neurological						
Convulsions	III	2		1		
Partial Seizures	II	1				
Mental Impairment	I	1				
Photopsia	I	1				
Somnolence	II	1				
Infectious						
UTI	II	1				

Progression and Survival
- Median Time to Progression (Days): 61 (29 -150)
- Median Survival (Days): 140 (97-989)

-2 patients with stable response
-2 patients with extended survival: 673 and 989 days
-Encouraging results scattered throughout cohorts, suggests tumor characteristics and not dose correlate with tumor response

Conclusions

- No Significant Adverse Events probably or definitely related to viral infusion.
- 1 episode of convulsions possibly attributed to viral infusion.

Tolerability of Reovirus Infusion
- No DLT reached in current study
- Limited adverse event profile

Efficacy of Reovirus infusion
- Two patients with stable response
- One patient with survival nearly 3 years

Reovirus infusion for recurent malignant gliomas was found to be both safe and effective and warrants additional study