Dose-Finding and Safety Study of an Oncolytic Polio/Rhinovirus Recombinant against Recurrent Glioblastoma

John H. Sampson MD PhD; Annick Desjardins MD, FRCPC; Katherine B Peters MD, PhD; Tulika Ranjan MD; Gordana Vlahovic MD,; Denise Lally-Goss NP; Stevie Threatt; James Herndon PhD; Allan H. Friedman MD; Henry Friedman MD; Darell Bigner; Matthias Gromeier MD

INTRODUCTION

Current therapies for glioblastoma (GBM) are limited by ineffective delivery beyond the blood-brain barrier, limited diffusion of regionally-delivered macromolecules, and lack of tumor specificity. Sustained direct intracerebral infusion at slow flow rates [convection-enhanced delivery (CED)] can overcome delivery barriers. The prototype oncolytic poliovirus recombinant (PVS-RIPO) is the live attenuated, oral (SABIN) serotype 1 poliovirus vaccine containing a heterologous internal ribosomal entry site stemming from human rhinovirus type 2. Poliovirus' unique reliance on an unorthodox method of protein synthesis initiation at viral genomes enables genetic engineering of safe recombinants with high tumor cytolytic potential.

This is the first clinical use of poliovirus against cancer and first strategy targeting the polio receptor, nectin-like molecule-5 (Necl5/CD155), an oncofetal cell adhesion molecule and tumor antigen widely expressed ectopically in malignancy and associated with neoplasia. Due to Necl5 expression, neoplastic cells arising in the central nervous system are susceptible to polio infection and killing, providing the rationale for targeting cancer with poliovirus.

OBJECTIVES

Study objectives are to: determine the maximum tolerated dose and dose limiting toxicities of PVS-RIPO when delivered intracerebrally by CED; estimate progression-free survival and overall survival in recurrent GBM patients; obtain correlative mechanistic evidence for PVS-RIPO's effects on infected GBM tumors; and obtain information about clinical response rates to intratumoral inoculation of PVS-RIPO.

METHODS

Adult Patient Inclusion Criteria:

- 1-5 cm of measurable supratentorial recurrent GBM >=1cm away from the ventricles; >=4 weeks after chemotherapy, bevacizumab or study drug; adequate hematologic, hepatic and renal function; Karnofsky Performance Score (KPS) >=70%; boost immunization with trivalent inactivated IPOL™ (Sanofi-Pasteur) at least 2 weeks prior to administration of study agent; signed informed consent

METHODS (continued)

Adult Patient Exclusion Criteria:

- Pregnant or breast-feeding; impending, life-threatening cerebral herniation; known immunosuppressive disease or known human immunodeficiency virus infection; unstable or severe intercurrent medical conditions; albumin or gadolinium allergy; previous history of poliomyelitis or multifocal and/or leptomeningeal disease; patients who have not recovered from the toxic effects of prior therapy; Investigational drugs or immunotherapy <=4 weeks; IgG levels <400 mg/dL [4 g/L], undetectable anti-tetanus toxoid IgG, known history of agammaglobulinemia

Drug Delivery and Doses:
PVS-RIPO delivered intratumorally by CED over 6.5 hours. Dose escalation accomplished by increasing agent concentration, allowing flow-rate and infusion volume to remain constant. Two-step continual reassessment method used for dose escalation, with 1 patient each treated on dose levels 1-4, and a possibility of <=13 patients on dose level 5. PVS-RIPO is cGMP manufactured by NCI-SAIC (IND; no. 14,735).

Statistical Methods:
Overall survival (OS) was calculated from the date study treatment started until the date of death or date of last follow-up if alive. Progression-free survival (PFS) was calculated from the date study treatment started until the date of progression (or the date of death if death occurred before progression) or the date of last follow-up if alive. Kaplan-Meier methods were used to estimate median overall and progression-free survival for all patients.

RESULTS

A total of 8 patients have been treated. Median follow-up for all patients is 7.3 months (95% CI: 1.8, 14.1). Median PFS is 4.0 months (95% CI: 0.9, 8), and median OS is not estimable (see Figures 1 and 2). Six-month PFS is 48.6% (95% CI: 7.7%, 81.6%), and 6-month OS is 60.0% (95% CI: 12.6%, 88.2%). One patient has had a complete or partial response to date, thus the objective response rate is 12.5% (95% CI: 0.1%, 49.2%).

Study-related adverse events have included hemiparesis, diarrhea, seizure, vomiting, lethargy, headache, cough, nasal congestion and fever.

RESULTS (continued)

Figure 1. Progression-free survival for all patients

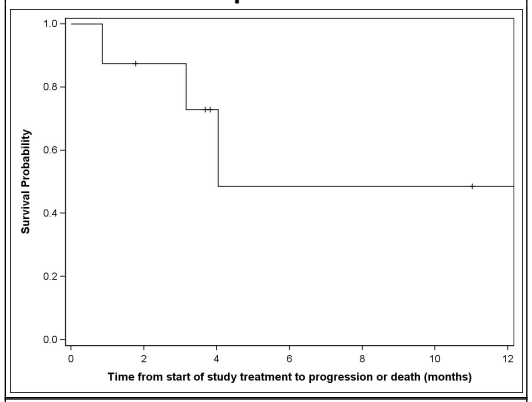
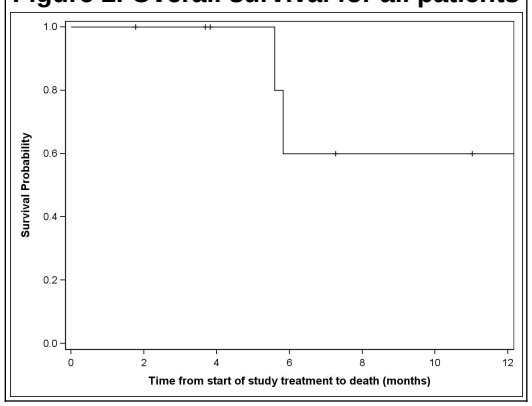
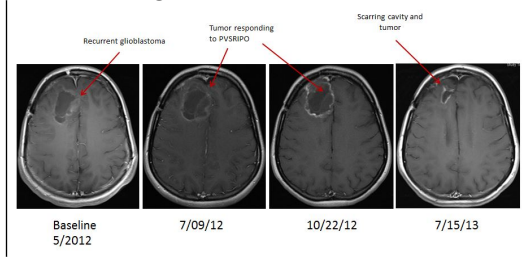


Figure 2. Overall survival for all patients

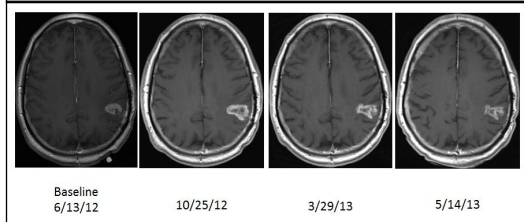


All patients enrolled are scheduled for clinical and radiological follow-up at 4, 8, 16, 24, 32, 40 and 48 weeks post PVS-RIPO. This includes a history and physical and neurological examination as well as KPS scoring. MRIs are obtained at each appointment and supplemented with PET scans, if indicated. Figure 3 shows patient MRIs.

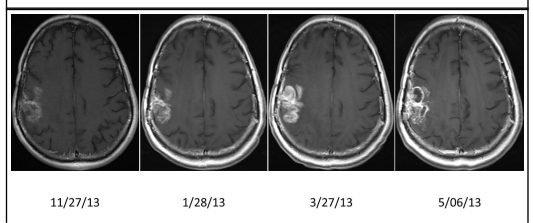
Figure 3. Patient MRIs



Patient 1, dose level 1



Patient 2, dose level 2



Patient 5, dose level 5

Patients 1 and 2: Initial worsening on imaging 2-4 months post-PVS-RIPO infusion, followed by an improvement; both remained neurologically stable throughout the course. Patient 5: Clinical and radiographic worsening 4 months post-PVS-RIPO infusion. Biopsy obtained at that time confirmed tumor recurrence. One month later, after FDA and IRB approval for re-treatment, imaging and pathology showed a vast majority of post-therapeutic effect, despite the fact that the patient received no treatment during that month. Further tissue analysis is ongoing.

CONCLUSIONS: PVS-RIPO infusion via CED is safe thus far. Initial MRI worsening seems to improve over time. Tumor innate responses do not impair PVS-RIPO oncolytic efficacy. Direct viral killing of neoplastic cells may eliminate some tumor burden, but it is yet unclear what the precise mechanism of oncolytic virotherapy with PVS-RIPO is. Much empirical evidence, however, implies host inflammatory responses in the therapeutic effects of oncolytic virotherapy. Imaging and pathologic evaluation of patient 5 seems to support this hypothesis.