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Clinical Investigation

A Phase 2 Study of Concurrent Radiation Therapy, Temozolomide, and the Histone Deacetylase Inhibitor Valproic Acid for Patients With Glioblastoma

Andra V. Krauze, MD,* Sten D. Myrehaug, MD,† Michael G. Chang, MD,‡ Diane J. Holdford,‡ Sharon Smith,* Joanna Shih, MD,* Philip J. Tofilon, PhD,* Howard A. Fine, MD,§ and Kevin Camphausen, MD*

**Radiation Oncology Branch, National Cancer Institute/National Institutes of Health, Bethesda, Maryland; †Department of Radiation Oncology, Lakeridge Health Durham Regional Cancer Centre, Oshawa, Ontario, Canada; ‡Massey Cancer Center Virginia Commonwealth University, Richmond, Virginia; and §New York University Langone Medical Center, New York, New York*

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Summary

This is a report of a phase 2 trial of 37 patients with newly diagnosed glioblastoma treated with valproic acid (VPA) at a dose of 25 mg/kg divided into 2 daily doses, concurrent with radiation and temozolomide therapy. VPA toxicity was comparable with historical data. Median overall survival and progression-free survival were 29.6 months and 10.5 months, respectively.

Purpose: Valproic acid (VPA) is an antiepileptic agent with histone deacetylase inhibitor (HDACi) activity shown to sensitize glioblastoma (GBM) cells to radiation in preclinical models. We evaluated the addition of VPA to standard radiation therapy (RT) plus temozolomide (TMZ) in patients with newly diagnosed GBM.

Methods and Materials: Thirty-seven patients with newly diagnosed GBM were enrolled between July 2006 and April 2013. Patients received VPA, 25 mg/kg orally, divided into 2 daily doses concurrent with RT and TMZ. The first dose of VPA was given 1 week before the first day of RT at 10 to 15 mg/kg/day and subsequently increased up to 25 mg/kg/day over the week prior to radiation. VPA- and TMZ-related acute toxicities were evaluated using Common Toxicity Criteria version 3.0 (National Cancer Institute Cancer Therapy Evaluation Program) and Cancer Radiation Morbidity Scoring Scheme for toxicity and adverse event reporting (Radiation Therapy Oncology Group/European Organization for Research and Treatment).

Results: A total of 81% of patients took VPA according to protocol. Median overall survival (OS) was 29.6 months (range: 21-63.8 months), and median progression-free survival (PFS) was 10.5 months (range: 6.8-51.2 months). OS at 6, 12, and 24 months was 97%, 86%, and 56%, respectively. PFS at 6, 12, and 24 months was 70%, 43%, and 38% respectively. The most common grade 3/4 toxicities of VPA in conjunction with RT/TMZ therapy were blood and bone marrow toxicity (32%),

Reprint requests to: Kevin Camphausen, Radiation Oncology Branch, National Cancer Institute, 10 Center Dr, Bldg 10, CRC, Rm B2-3561, Bethesda, MD 20892. Tel: (301) 496-5457; E-mail: camphauk@mail.nih.gov

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neurological toxicity (11%), and metabolic and laboratory toxicity (8%). Younger age and class V recursive partitioning analysis (RPA) results were significant for both OS and PFS. VPA levels were not correlated with grade 3 or 4 toxicity levels.
Conclusions: Addition of VPA to concurrent RT/TMZ in patients with newly diagnosed GBM was well tolerated. Additionally, VPA may result in improved outcomes compared to historical data and merits further study. Published by Elsevier Inc.

Introduction

Primary brain tumors represent 2% of tumor subtypes; 23,000 new cases and 14,000 deaths per year were registered in the United States, with grade 4 glioblastoma (GBM) being the most common. Standard therapy consists of maximal safe resection followed by concurrent radiation therapy (RT) and temozolomide (TMZ), followed by adjuvant TMZ, which results in an overall survival (OS) of 27.2% at 2 years and 9.8% at 5 years (1). Although the efficacy of this therapy remains limited, attempts to increase the effectiveness of the RT/TMZ protocol (2, 3) have not been successful.

The pattern of recurrence following combined RT/TMZ therapy indicates failure in or adjacent to the initial RT treatment volume, suggesting that enhancing the effectiveness of RT could lead to an improved therapeutic response. A number of strategies for modifying the delivery of RT (4-6) have been tested, without an improvement in survival. Integration of cytotoxic agents as radiation modifiers into GBM treatment protocols (7) has been disappointing. An increased understanding of the mechanisms mediating radiation-induced cell death has led to the use of molecularly targeted agents such as histone deacetylase inhibitors (HDACi) (8, 9). HDACs comprise a family of enzymes that remove acetyl groups from histones as well as other nuclear and cytoplasmic proteins. Inhibition of HDAC activity has been shown to selectively increase tumor cell radiation sensitivity in a variety of in vitro models and to enhance radiation-induced growth delay of subcutaneous human tumor xenografts (8-10). HDACi also reduce the repair of DNA double-strand breaks, a process critical to radiation-induced cell death and consistent with radiation sensitization (8, 9).

Valproic acid (VPA), a nonhepatic enzyme-inducing antiepileptic drug, is of particular relevance because it enhances the radiation sensitivity of tumor cells by using in vitro and in vivo model systems (9, 11); it is orally bioavailable; it effectively crosses the blood-brain barrier; and its sera and plasma levels are routinely measured as an antiseizure drug (12). On the basis of the preclinical evidence of VPA as a radiation sensitizer and its reportedly safe long-term use as an antiepileptic agent, we initiated a phase 2 study designed to investigate the safety, tolerability, and effectiveness of concomitant RT/TMZ therapy and relatively high-dose VPA followed by adjuvant TMZ in patients with newly diagnosed GBM.

Methods and Materials

Patient eligibility

This open-label, phase 2 study (NCI-06-C-0112) was conducted at the National Cancer Institute (NCI) and Virginia Commonwealth University in patients with histologically confirmed GBM, who were 18 years of age or older, had a life expectancy greater than 8 weeks, and who had undergone surgery no more than 6 weeks prior to enrollment. Pathology review was obtained in all patients. Patients were required to have a Karnofsky performance status $\geq$60 and adequate hematological, renal, and hepatic function. Exclusion criteria included previous VPA therapy, chemotherapy, or RT treatment; a known disorder of urea metabolism; and any history of a second malignancy other than nonmelanoma skin cancer or cervical cancer $<$3 years since diagnosis. Concurrent use of sulfamethoxazole, salicylates, or naproxen was not allowed. The protocol was reviewed and approved by the NCI Institutional Review Board, and written, informed consent was signed by all patients.

Treatment

Patients received VPA, 25 mg/kg orally, divided into 2 daily doses, concurrent with RT and TMZ. No VPA was administered adjuvantly. A dose of 25 mg/kg was selected based on preclinical pharmacology (9). In mice, 150 mg/kg VPA would yield plasma levels of $\approx$225 μg/mL and brain levels of $\approx$60 μg/g of brain tissue (12); and in humans, 25 mg/kg would yield a plasma level of $\approx$125 μg/mL and brain levels of $\approx$40 μg/g. Because 25 mg/kg of VPA can be given safely in patients with acute mania, this dose was chosen for this study. The first dose of VPA was given 1 week before the first day of RT at 10 to 15 mg/kg/day and subsequently increased up to 25 mg/kg/day, as recommended to reduce side effects, over the week prior to RT (Fig. 1). RT was delivered using 3-dimensional (3D) conformal RT or intensity modulated RT technique 5 days per week in 2-Gy fractions to 60 Gy total. T2-weighted magnetic resonance imaging (MRI)-defined tumor volume and surrounding edema with a 2-cm margin received 46 Gy. T1-weighted MRI-defined tumor volume with a 2.5-cm margin received an additional 14 Gy. TMZ was given daily at a dose of 75 mg/m^2 concurrently with RT. Patients used inhaled pentamidine for PCP *Pneumocystis* pneumonia prophylaxis. Adjuvant TMZ was given for 5 days at 150 mg/m^2 for 1