

# Long-term Survival and Complete Response of a Patient With Recurrent Diffuse Intrinsic Brain Stem Glioblastoma Multiforme

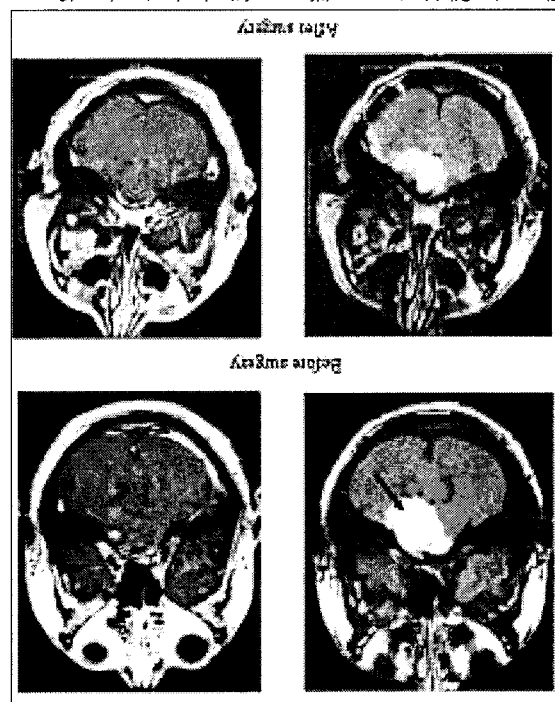
Stanislaw R. Burzynski, MD, PhD, Robert I. Lewy, MD, FACP, Robert Weaver, MD, Tomasz Janicki, MD, Gabor Jurida, MD, Mohammad Khan, MD, Chymbeelyn B. Larisma, MD, Jaroslaw Paszkowiak, MD, and Barbara Szymkowski, MD

Recurrent diffuse intrinsic brain stem glioblastoma multiforme carries an extremely poor prognosis and a median survival of less than 7 months. In this article, the authors report good results in a 40-year-old man diagnosed with glioblastoma multiforme who received antineoplastic therapy. The patient's brain tumor was diagnosed in May 1999, and he subsequently underwent subtotal tumor resection and standard radiation therapy. Magnetic resonance imaging and positron emission tomography scans documented his tumor recurrence. Approximately 2 months after completion of radiation therapy, he was admitted for administration of intravenous antineoplastic A10 and AS2-1 through a subclavian venous catheter by intermittent bolus injections 6 times per day using a portable pump. Administration of antineoplastic A10 and AS2-1 was over 655 consecutive days with the exception of a few short interruptions. The maximum dosage of A10 was 8.15 g/kg/d and AS2-1 0.35 g/kg/d. Antineoplastic A10 and AS2-1 administration was very well tolerated with only mild reversible side effects. Follow-up magnetic resonance imaging and positron emission tomography scans revealed decrease and eventually disappearance of the tumor. A complete response was documented after approximately 1 year of antineoplastic A10 and AS2-1 administration. More than 4 years later, off antineoplastic A10 and AS2-1, the patient is tumor free, able to carry on normal activities, and works full-time, and his Karnofsky Performance Status increased from 50 to 100. Extensive phase II trials with antineoplastic A10 and AS2-1 in patients with glioblastoma multiforme are nearing completion. These trials may provide more data regarding the efficacy of antineoplastic A10 and AS2-1 in the treatment of glioblastoma multiforme in untreated patients compared to the results in those patients with tumor recurrence after radiation therapy.

**Keywords:** brain stem glioma; GBM; brain tumor; glioma; antineoplastic; phenylacetate; phenylbutyrate

SRB, RW, GJ, and BS are at the Department of Internal Medicine; RIL and CBL are at the Department of Medical Oncology; TJ is at the Department of Medical Documentation/Data Processing; and MK is at the Department of Radiology, Burzynski Clinic, Houston, Texas. JP is at the Department of Quality Assurance, Burzynski Research Institute, Houston, Texas.

**Correspondence:** Stanislaw R. Burzynski, MD, PhD, Burzynski Clinic, 9432 Old Katy Road, Suite 200, Houston, TX 77082. E-mail: info@burzynskclinic.com.



**Figure 1** Glioblastoma multiforme of the brain stem in a 40-year-old man that recurred after partial resection and radiation therapy. T2-weighted (left row) and T1-weighted gadolinium-enhanced (right row) magnetic resonance images of the head. Images in the upper row show the tumor before partial resection, and images in the lower row were performed after partial resection, but prior to radiation therapy.

## Case Report

The patient is a 40-year-old Caucasian man who was evaluated in Singapore in May of 1999 after he developed progressive numbness of the left forehead, dryness of the left eye, facial weakness, and numbness of the right upper and lower extremities. Magnetic resonance imaging (MRI) of the head showed a mass involving the pons and brachium pontis with an area of contrast enhancement. The enhancing characteristics changed over a period of 10 days, with decreased enhancement on the patient's MRI of the head performed on June 1, 1999, at M. D. Anderson Cancer Center (MDA) in Houston, Texas. Just after he returned to the United States. The patient was further evaluated and underwent a left suboccipital craniotomy with subtotal resection of the pontine tumor at MDA on June 2, 1999, per Raymond Sawaya, MD, chairman of the Department of Neurosurgery. The

pathological diagnosis was GBM per MDA's neuro-pathologist, Janet M. Bruner, MD (which was also reviewed by Raymond Sawaya, MD). After the surgery, the patient had some increased left-sided numbness of the face, intermittent diplopia, left facial nerve paralysis, and imbalance. Postoperative MRI of the head revealed residual tumor and postoperative changes (Figure 1). Between June 18, 1999, and August 2, 1999, he underwent radiation therapy at MDA and received 5400 cGy in 30 fractions. Follow-up MRIs of the head of August 23, 1999, and September 22, 1999 (51 days after completion of radiation therapy), confirmed tumor recurrence. Treating physicians at MDA informed the patient that his tumor could not be cured and he may have no longer than 6 months to live, with or without chemotherapy.

On September 30, 1999, 8½ weeks after completion of his radiation therapy, the patient was admitted for administration of ANP based on a special exception to protocol BT-11.<sup>3</sup> At that time, he was found to have right hemiparesis, walking and balance difficulties, vertigo, diplopia, left facial nerve paralysis, a visual field deficit in the left upper quadrant of the left eye, hearing distortion in the left ear, slurred speech, shortness of breath, and indigestion. He required considerable assistance and frequent medical care, and his KPS was determined to be 50. The patient signed the consent form, which was reviewed by the Food and Drug Administration (FDA) and approved by the Institutional review board (IRB). The treatment was supervised by the IRB, the membership of which was in agreement with the FDA. The administration of ANP and assessment of safety and efficacy of ANP was previously described.<sup>3</sup>

Both formulations of ANP were administered intravenously through a Broviac subclavian venous catheter in gradually escalating doses by intermittent bolus injections (6 times a day) using a portable Provider 6000 dual channel pump (Abbott Laboratories, North Chicago, Ill, USA). The dosage of antineoplastic A10 was gradually increased to 8.15 g/kg/d and AS2-1 to 0.35 g/kg/d. The patient received 655 days of total treatment. After the initial 54 days, the dosage of A10 was decreased to an average of 5.29 g/kg/d and AS2-1 to 0.25 g/kg/d. On several occasions, ANP was discontinued from 1 to 3 days due to mild hypernatremia (from 148 mEq/L to 151 mEq/L). The patient was also off ANP for 2 days due to increased fatigue. On March 29, 2000, his white blood cell count (WBC) decreased to  $2.5 \times 10^3/\text{mm}^3$ ; therefore, he discontinued ANP and was given filgrastim 0.3 mg subcutaneously (SC) daily for 3 days. At that time, his WBC rose to  $6.6 \times 10^3/\text{mm}^3$ , and ANP was restarted. On June 30, 2000, his hemoglobin decreased to 9.0 g/dL, and he was given epoetin alfa 10,000 units SC every other day

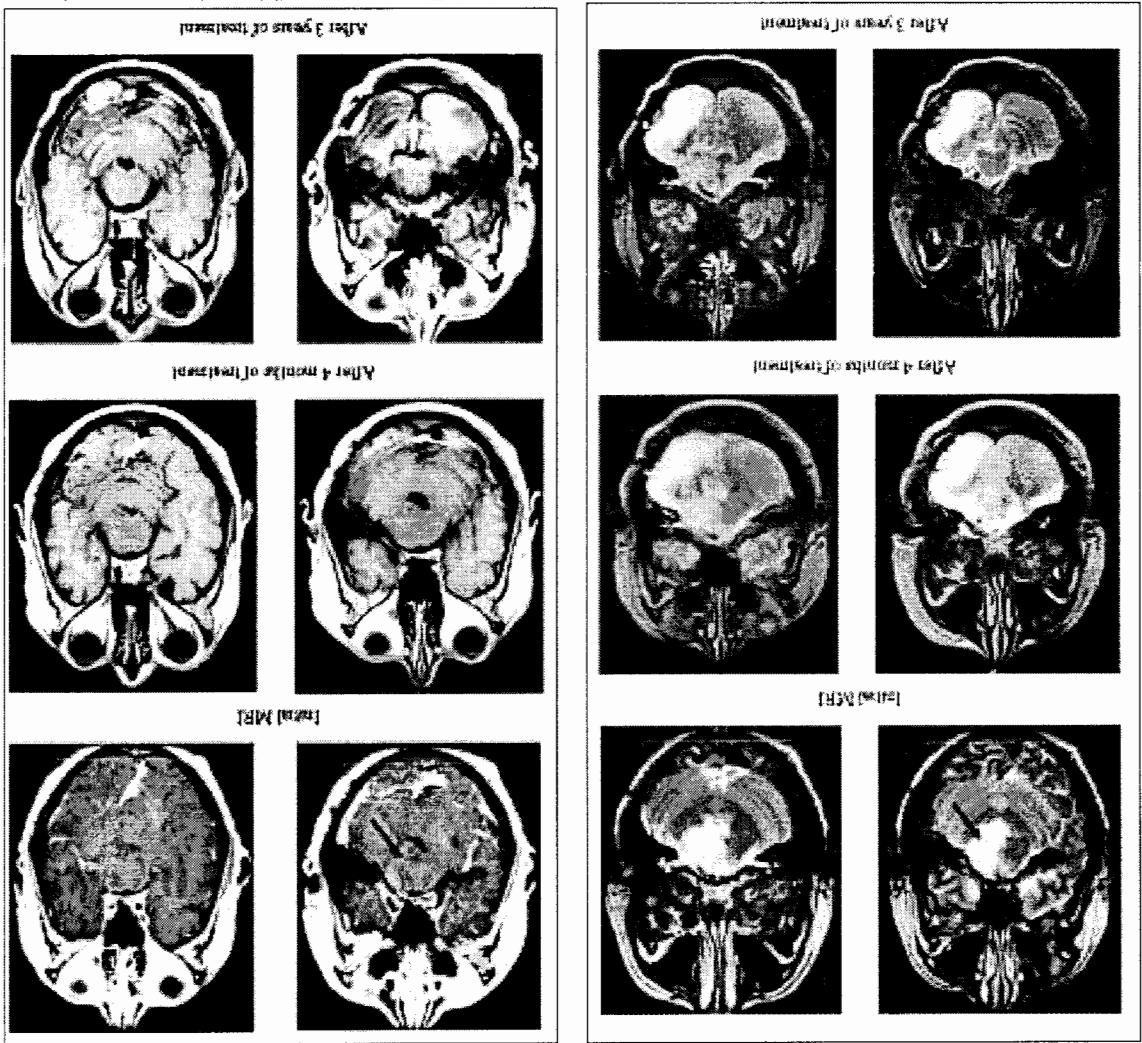


Figure 3 A T1-weighted gadolinium-enhanced magnetic resonance image of the head corresponding to T2-weighted images shown in Figure 2.

Figure 2 A T2-weighted magnetic resonance image of the head of the patient from Figure 1. Images in the upper row show a large tumor that progressed after radiation therapy and prior to antiangiogenesis (ANP) administration. Images in the middle and lower rows show a marked decrease in the tumor size after administration of ANP.

a gastroenterologist, but there were no pathological findings except for changes related to obesity. ANP was permanently discontinued on August 21, 2001, due to resolution of the tumor. Concomitant medications included allolupinol, pravastatin (for preexisting hypercholesterolemia), dexamethasone, ranitidine, and temazepam. Pravastatin was discontinued on October 27, 1999; allolupinol on February 22, 2000; dexamethasone on April 20, 2000; and ranitidine and temazepam on April 26, 2000. It is not believed that low-dose dexamethasone (median dose 4 mg/d), taken pre-treatment and continued for approximately 6 months, substantially contributed to his duration of survival.

for 10 days. On July 10, 2000, the WBC decreased to  $2.6 \times 10^3/\text{mm}^3$ . ANP was again discontinued, and the patient received filgrastim  $0.3 \text{ mg SC}$  daily for 3 days. On July 13, 2000, his WBC rose to  $27.3 \times 10^3/\text{mm}^3$  and hemoglobin to  $10.1 \text{ g/dL}$ , and ANP was restarted. On July 15, 2000, ANP was discontinued due to elevation of transaminases (serum glutamic oxaloacetic transaminase  $736 \text{ U/L}$ ; serum glutamic pyruvic transaminase  $689 \text{ U/L}$ ). On July 28, 2000, the transaminases had returned to acceptable ranges, and ANP was restarted on July 31, 2000. In August of 2001, the patient developed persistent diarrhea and was evaluated by

sults, with 1 case of a complete response and 4 cases of stable disease.<sup>9</sup>

Combination treatment with A10 and AS2-1 (active ingredients PG, isoptG, and PN) provided better results than with A10 or AS2-1 individually.<sup>12,10,11</sup> Buckner et al obtained no response to A10 and AS2-1 in their limited study, which involved only 6 evaluable patients (most of them with GBM).<sup>12</sup> Three phase II studies confirmed the necessity of extended administration of high doses of A10 and revealed 30%, 44%, and 50% objective responses (complete and partial responses).<sup>9,10,11</sup> The main difference between Buckner et al's study and these studies is the dosage of A10, which was approximately 50 times lower in Buckner et al's study, whereas the average maximum dosage of AS2-1 was the same.<sup>13</sup>

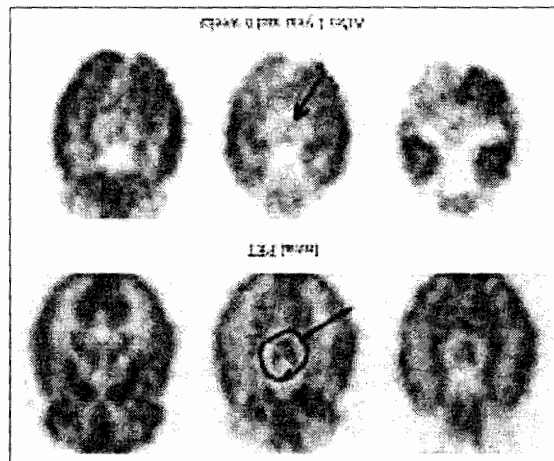
An important issue for discussion is the possible contribution of radiation therapy to the long-term control of the disease. In this patient, radiation therapy was completed more than 8 weeks before beginning ANP, and its failure was confirmed by tumor recurrence on MRI of the head performed 51 days after completion of radiation. Also, follow-up PET, performed 14 weeks after completion of radiation, continued to show an active hypermetabolic tumor (Figure 4).

It is not unusual to accept patients to a phase II study 8 weeks post radiation therapy, such as in a recent phase II study of recurrent GBM conducted in the 10 leading brain tumor treatment centers, in which the patients were admitted at least 4 weeks post radiation therapy. In one study, the median survival for intravenous carboplatin with blood-brain barrier disruption was 6½ months.<sup>1</sup>

It is unlikely that radiation therapy alone is the cause of long-term survival in this patient; however, we cannot exclude the possibility of the synergistic effects of radiation therapy followed by ANP. Phase II studies of 2 groups of patients with GBM are currently nearing completion comparing results of patients receiving ANP after radiation therapy failure to patients receiving ANP without prior radiation therapy, which may provide the answer to the above question. This case report may also have important consequences because it describes the successful treatment of a highly aggressive malignant tumor with a poor prognosis to cation in the brain stem.

The mechanism of action of ANP is believed to occur on a molecular level, affecting the genes involved in the formation of brain tumors by decreasing expression of the oncogenes *AKT2*, *RAS*, and *MYC* and activating the tumor suppressors *TP53*, *p21*, *PTEN*, and *INM*.<sup>12,11,13</sup> The 3 active ingredients that constitute

Figure 4. Positron emission tomography scan of the brain initially and after approximately 15 months of antineoplastic administration, which confirms disappearance of the hypermetabolic lesion.



Follow-up MRIs of the head at 8-week intervals showed a continuous decrease of the size of the tumor. Figures 2 and 3 show the initial and follow-up MRIs of the head after 4 months and 3 years, respectively, and document marked decrease of the tumor size. The patient's response was also followed by repeat positron emission tomography (PET) scan to determine the viability of the tumor and confirm the response. On December 20, 2000, the patient's results were classified as complete response based on the PET, which showed no hypermetabolic lesions. Figure 4 shows PET of the brain initially and after approximately 15 months of ANP administration and confirms the disappearance of the hypermetabolic lesion. (MRI and PET scans were performed and reviewed at MDA.) The most recent clinical evaluation of December 1, 2003, showed the patient in good condition and complaining only of minor symptoms including slight balance difficulties, decreased lacrimation in the left eye, left-sided facial muscle weakness, and slight short-term memory deficit. The patient is able to carry on normal activities and works full-time (KPS = 100). The most recent MRI of the head of November 26, 2003, did not reveal tumor recurrence.

## Discussion

Active ingredients of A10 and AS2-1 (PN and PG) have been tested separately in clinical trials; however, they have either failed or showed only some activity in patients with recurrent malignant gliomas.<sup>23</sup> A phase I study of PB in 22 patients provided more optimistic re-

7. Burzynski SR. Phase I clinical studies of antineoplasia AS2-5 injections. In: Ishigami J, ed. *Recent Advances in Chemotherapy*. Tokyo, Japan: University of Tokyo Press; 1985:586-587.
8. Chang SM, Rubin JC, Robins III. Phase II study of phenylacetate in patients with recurrent malignant glioma: a North American Brain Tumor Consortium report. *J Clin Oncol*. 1999;17:984-990.
9. Fisher JD, Carlucci MA, Baker SD, et al. The NABTT CNS Consortium. Dose escalation study of oral sodium phenylbutyrate (PB) with refractory high-grade astrocytoma (HGA): maximum tolerated dose (MTD), toxicity profile, pharmacology and survival [abstract]. *Proc Am Soc Clin Oncol* 2000;19:166a.
10. Burzynski SR, Kubove E, Burzynski B. Phase II clinical trials of antineoplasia A10 and AS2-1 infusions in astrocytoma. In: Adam D, ed. *Recent Advances in Chemotherapy*. Munich, Germany: Futuramed; 1992:2506-2507.
11. Burzynski SR, Conde AB, Peters A, et al. A retrospective study of antineoplasia A10 and AS2-1 in primary brain tumors. *Clin Drug Invest*. 1999;18:1-10.
12. Buckner JD, Malkin MG, Reed E. Phase II study of antineoplasia A10 (NSC648539) and AS2-1 (NSC6200261) in patients with recurrent glioma. *Mayo Clin Proc*. 1999;74:137-145.
13. Burzynski SR. Efficacy of antineoplasia A10 and AS2-1. *Mayo Clin Proc*. 1999;74:641-642.
14. Burzynski SR, Waldbing R. Mechanism of action, uptake, and gene array studies on the antineoplastic agent phenylacetate. *Neuro-oncol*. 2003;5:309.
15. Waldbing RJ, Patel S, Burzynski SR. Uptake and intracellular binding of the antineoplastic agent phenylacetic acid (PA) and phenylacetate (PGA): effects on epigenetic mechanisms of gene regulation and gene expression. Report to the US Food and Drug Administration. May 26, 2004.
1. Prados MD, Schold CJ, Fine HA, et al. A randomized, double-blind, placebo-controlled, phase 2 study of RMP-7 in combination with carboplatin administered intravenously for the treatment of recurrent malignant glioma. *Neuro-oncol* 2003;5:96-103.
2. Baker MJ, Brem S, Sherman B, Phuphanich S. Complete response of a recurrent, multicentric malignant glioma in a patient treated with phenylbutyrate. *J Neurooncol* 2003;59:239-242.
3. Dover C, Brustlow S, Samid D. Increased fetal hemoglobin in patients receiving sodium 4-phenylbutyrate. *N Engl J Med*. 1992;327:569-570.
4. Burzynski SR. Potential of antineoplasia in diseases of old age. *Drugs Aging*. 1993;7:157-167.
5. Burzynski SR, Lewy RJ, Weaver RA, et al. Phase II study of antineoplasia A10 and AS2-1 in patients with recurrent diffuse intrinsic brain stem glioma (preliminary report). *Drugs R D*. 2003;4:91-101.
6. Burzynski SR, inventor. Purified antineoplasia fractions and methods of treating neoplastic disease. US patent # 470 970. September 11, 1981.

## References

The authors express their appreciation to Drs L. M. Iamki and J. Pleasure for evaluation of the MRI and PET films.

## Acknowledgments

The authors express their appreciation to Drs L. M. Iamki and J. Pleasure for evaluation of the MRI and PET films.

ANP influence multiple signaling pathways and thereby provide a broad spectrum of activity that results in long-term complete responses in patients with malignancies not curable by standard treatments.