

## Review Article

# Recurrent/Persistent Glioblastoma: Complete Response and 24 Years Disease-free Survival in a 45-Year-Old Female Treated with Antineoplastons (Successful Treatment of Glioblastoma with Antineoplastons)

Stanislaw R. Burzynski\*, Gregory S. Burzynski, Tomasz J. Janicki and Samuel W. Beenken

Katy Freeway, Houston, Texas, USA

\*Corresponding author: Stanislaw R. Burzynski, MD, PhD 9432 Katy Freeway, Houston, Texas, USA; Tel: 713-335-5697; Fax: 713-335-5658

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## Abstract

**Rationale:** Glioblastoma (GBM), which accounts for 48% of all malignant central nervous system (CNS) tumors and 57% of gliomas, has a very poor prognosis. Patients with recurrent/persistent GBM after standard therapy usually die within six months. The case of an adult female with a recurrent/persistent GBM is presented here to detail/discuss the efficacy of ANP therapy (Antineoplaston A10 {Atengenal} and Antineoplaston AS2-1 {Astugenal}) in the treatment of this disease. **Objectives:** This patient was treated at the Burzynski Clinic (BC), as a Compassionate Exemption (CE) according to the Phase II Protocol, BT-20, which utilized ANP therapy in the treatment of patients with GBMs. ANP therapy was delivered via subclavian catheter and infusion pump and then by mouth. Tumor response was measured by sequential magnetic resonance imaging (MRI) of the brain utilizing gadolinium enhancement. **Findings:** This patient was diagnosed with GBM of the right temporoparietal region in May 1997, at age 45, and underwent two surgical resections, radiation therapy (RT), and gamma knife ablation elsewhere. At age 46 years and eight months, she presented to the BC with recurrent/persistent disease. She complained of weakness, dizziness, short-term memory loss, and nausea. She had difficulty speaking and walked with assistance due to discoordination and left-sided weakness. Baseline brain MRI at the BC revealed a measurable enhancing nodule in the surgical bed. ANP therapy was initiated in August 1998 and the patient achieved a complete response (CR) within five months. Now, 24 years later, the patient is doing well and showing no evidence of tumor recurrence. **Conclusions:** The utilization of ANP therapy to obtain a cure in a patient with recurrent/persistent GBM is presented. We conclude that ANP therapy is an attractive therapeutic option for adults with a GBM who are ineligible for or refuse standard therapy or demonstrate recurrent/persistent disease after standard therapy.

**Keywords:** Brain tumor, Glioblastoma, Persistent glioblastoma, Recurrent glioblastoma, Phase II studies

## Introduction

Glioblastoma (GBM), the most common malignant central nervous system (CNS) tumor, accounting for 48% of all malignant tumors and 57% of gliomas, has a very poor prognosis [1]. Long term-survival is rare. Patients with recurrent/persistent GBM after standard therapy usually die within six months. Radiation therapy (RT) and chemotherapy therapy have not significantly affected outcome. Negative prognostic factors include advanced age, low Karnofsky Performance Status (KPS), and less than a gross total resection at initial surgery [2,3]. The overall survival (OS) rate at five years has remained constant for two decades at 5.8% [1,4,5].

Exposure to ionizing radiation [6], and the Li-Fraumeni and Lynch syndromes (<1% of cases) [7] are risk factors for GBM. Based on registry data from 2011 through 2015, the annual age-adjusted incidence of GBM is 3.2 per 100,000 population in the United States while the overall prevalence is 9.2 per 100,000 population [1]. The male: female ratio is 1:4.

Isocitrate dehydrogenase (IDH) enzymes participate in several major

metabolic processes, such as the Krebs cycle, glutamine metabolism, lipogenesis and redox regulation [8-10]. Concerning the diagnosis of GBM, the 2016 revision of the World Health Organization (WHO) of CNS tumors, included IDH status, which resulted in three sub-groups, IDH-wild-type, IDH-mutant, and not otherwise specified (NOS) [11,12]. IDH-wild-type GBM is characterized by de novo development with no identifiable precursor lesion and represents 90% of patients with GBM [12]. On the other hand, IDH-mutant GBM, typically arises from a precursor diffuse or anaplastic astrocytoma and represents 10% of patients with GBM [12]. O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is seen in 30-50% of IDH-wild-type GBMs and may allow a better response to alkylating chemotherapy, especially temozolomide, providing for a better prognosis [13].

Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain is used in the diagnosis and follow-up of GBM. T2-weighted, T2-fluid attenuated inversion recovery (T2-FLAIR), T1 weighted, and T1-weighted contrast-enhanced images are obtained. GBMs are gadolinium-enhancing and sequential T1-weighted contrast-enhanced images are utilized to determine the effect of therapy [14,15].

We present here the successful use of ANP therapy (Antineoplaston A10 {Atengenal} and Antineoplaston AS2-1 {Astugenal}) in the treatment of recurrent/persistent GBM in a 46 year and eight-month-old female, initially diagnosed at age 45 and treated with gross total resection, radiation therapy (RT), gamma knife ablation of recurrent tumor, and subsequent right lobectomy elsewhere. We also present the use of targeted therapy in the treatment of GBM, including our own preliminary results.

## Materials and Methods

ANP research began in 1967, when significant deficiencies were noticed in the peptide content of the serum of patients with cancer compared with healthy persons. Initially ANP were isolated from the blood and later from urine [16]. Subsequent studies of the isolated ANP demonstrated that Antineoplaston A-10 and Antineoplaston AS2-1 were the most active ANPs. The chemical name of Antineoplaston A-10 is 3-phenylacetyl-amino-2,6-piperidinedione. It consists of the cyclic form of L-glutamine connected by a peptide bond to phenylacetyl residue. When given orally, Antineoplaston A10 resists the attack of gastric enzymes. In the small intestine, under alkaline conditions, 30% is digested into phenylacetylglutamine (PG) and phenylacetylglutamate (isoPG) in a ratio of approximately 4:1. The mixture of synthetic PG and isoPG in a 4:1 ratio, dissolved in sterile water constitutes Antineoplaston A10 intravenous (IV) injection. Further metabolism of Antineoplaston A10 results in phenylacetate (PN). Both metabolites PG and PN have anticancer activity. The mixture of PN and PG in a 4:1 ratio, dissolved in sterile water constitutes Antineoplaston AS2-1 IV injection [17].

This patient was 45-years-old when she presented to a local hospital with a several month history of frequent headaches followed by left-sided weakness. Magnetic resonance imaging (MRI) of the brain showed a tumor in the right temporoparietal region. In May 1997, she underwent gross total resection of the tumor. Pathological examination of the microscopic slides from the submitted surgical specimen showed a GBM. The patient then received RT at a dose of

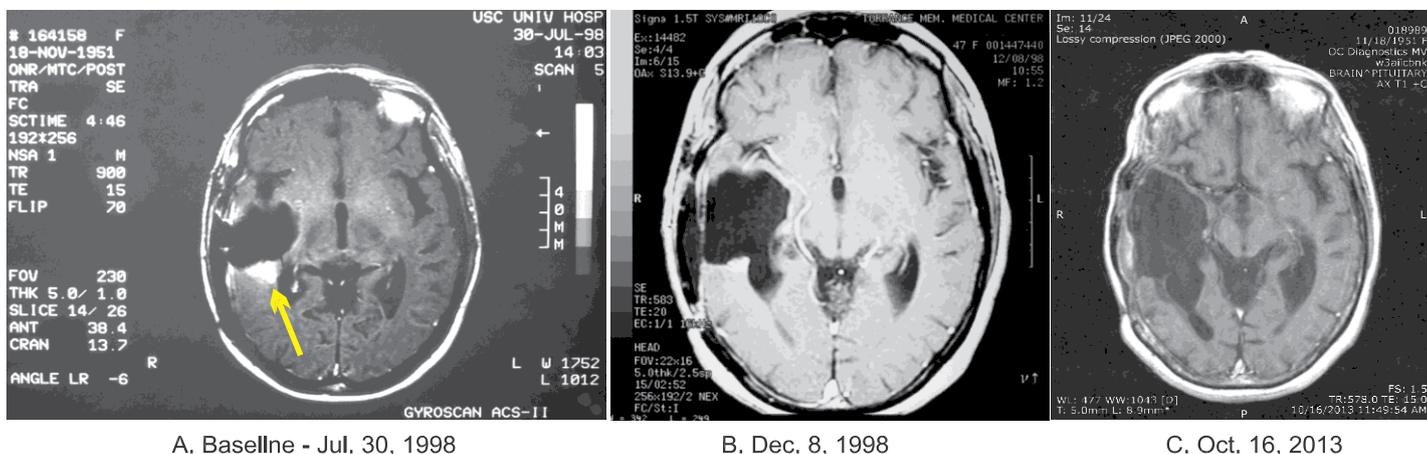
5940 cGy over 6 weeks. Six months later, she underwent gamma knife ablation of recurrent tumor. Seven months later, MRI of the brain MRI showed an enhancing lesion in the right temporal region. At that time, the patient underwent a right temporal lobectomy elsewhere. Histological examination of the surgical specimen provided a diagnosis of GBM. This was confirmed by positron emission tomography (PET). The patient was advised to undergo a third operation, but she refused and elected to be treated at the Burzynski Clinic (BC). MRI of the brain performed on July 30, 1998 showed a 1.3 cm x 1.2 cm (volume = 1.56 cm<sup>3</sup>) enhancing nodule in the surgical bed (Figure 1).

During her baseline evaluation at the BC, the patient complained of weakness, dizziness, short-term memory loss, discoordination, and nausea. She was found to have difficulty speaking and could not walk without assistance due to discoordination and left-sided weakness. Both optical discs were blurred. Karnofsky Performance Status (KPS) was 50. On August 10, 1998, the patient began ANP therapy according to Protocol BT-20, "Antineoplaston Therapy in Treating Adults with Residual/Recurrent/Progressive Glioblastoma Multiforme". Intravenous (IV) ANP therapy was delivered via a subclavian catheter and a programmable infusion pump.

This Phase II trial was conducted in accordance with the U.S. Code of Federal Regulations, Title 21, Parts 11, 50, 56 and 312; the Declaration of Helsinki (1964) including all amendments and revisions; the Good Clinical Practices: Consolidated Guideline (E6), International Conference on Harmonization (ICH) and Guidance for Industry (FDA). By participating in this study protocol, the investigators agreed to provide access to all appropriate documents for monitoring, auditing, IRB review and review by any authorized regulatory agency.

## Results

Response to ANP therapy was measured by serial brain MRIs, with and without gadolinium contrast. Tumor volume was calculated as the sum of the volume of all measurable lesions (>5 mm diameter) with imaging. The response criteria were as follows: a CR indicated complete disappearance of all enhancing tumor while a partial response (PR)



**Figure 1:** Axial MRI images of the brain: A - July 30, 1998 – Baseline magnetic resonance imaging (MRI) of the brain showing measurable enhancing tumor (see arrow), with a volume of 1.56 cm<sup>3</sup>, in the surgical bed of a temporal lobectomy. B - December 8, 1998 - MRI of the brain showing a complete response (CR) with no enhancing tumor seen. C - October 16, 2013 – Post-therapy MRI of the brain showing maintenance of the CR.

indicated a 50% or greater reduction in total enhancing tumor volume. CR and PR required a confirmatory brain MRI performed at least four weeks after the initial finding. PD indicated a 25% or greater increase in enhancing tumor volume, or new enhancing disease, while stable disease (SD) did not meet the criteria for PR or PD [15]. All brain MRIs were reviewed by a prominent outside radiologist. Consent was obtained from the patient for publication of the brain MRIs presented in this report.

The patient's starting dose of A10 was 1.23 g/kg/d and was gradually increased to 10.48 g/kg/d and subsequently reduced to 5.20 g/kg/d. Her starting dose of AS2-1 was 0.15 g/kg/d and was gradually increased to 0.17 g/kg/d. On December 8, 1998, MRI of the brain showed that the patient had achieved a complete response (Figure 1). IV ANP therapy was discontinued after 18.5 months [18-44].

Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE v.3). While receiving IV ANP therapy, the patient experienced two Grade 1 AEs possibly related to IV ANP therapy. Both resolved.

Once IV ANP therapy was completed, the patient began oral ANP therapy. The starting dose of both A10 and AS2-1 was 0.05 g/kg/d and both were gradually increased to 0.14 g/kg/d. All ANP therapy was discontinued 31 months from treatment start.

During the course of her ANP therapy, the patient made substantial clinical recovery. After 9 months of IV ANP therapy, she was able to walk with the help of a walker. Her KPS increased to 80. At 4 years after treatment completion, the patient was able to walk with a cane. Serial follow-up brain MRIs, with the latest performed in October 16, 2013, showed no recurrence of disease (Figure 1). At last follow-up (September 9, 2022), the patient was maintaining an excellent quality of life. The patient has not received any additional anti-tumor therapy since ANP therapy was discontinued and has consented to publication of the radiographs presented herein (Figure 2).



**Figure 2:** Photograph of the patient, on an exercise bicycle, following completion of ANP therapy and achievement of a complete response (CR).

## Discussion

Based on a Phase III study by R. Stupp and colleagues, published in 2005, standard therapy for GBM consists of maximal surgical resection, followed by 60 Gray (Gy) RT over 6 weeks with concomitant daily temozolomide followed by a further 6 cycles of maintenance temozolomide [18]. In patients with good performance status (KPS > 60), the median OS was 14.6 months for RT plus temozolomide vs. 12.1 months for RT alone ( $P < 0.001$ ).

After standard therapy, most patients recur within 6 months. In this setting, there is no standard-of-care systemic therapy. Alkylating chemotherapy is commonly used, including lomustine, carmustine, and additional temozolomide although the benefits are modest and only patients with MGMT promoter methylation are likely to benefit [19-21]. Salvage chemotherapy with combined procarbazine, lomustine, and vincristine may have some activity, although its use is limited by significantly greater toxicity [22,23]. The quality of data for individual chemotherapy agents or regimens is generally poor and comparison of studies is difficult.

The US Food and Drug Administration (FDA) granted accelerated approval to single-agent bevacizumab based solely on early phase 2 data indicating improved progression-free survival (PFS), although no OS benefit was seen [24,25]. Subsequent randomized phase 3 trials have demonstrated that bevacizumab in combination with lomustine improves PFS compared with lomustine alone (4.2 months vs. 1.5 months; [ $P < 0.001$ ]), but again, without any change in OS [26].

ANP therapy's mechanism of action differs from that of RT or cytotoxic chemotherapy. Growth of normal cells is controlled by cell cycle progression genes (oncogenes) and by cell cycle arrest genes (tumor suppressor genes). In cancer, alteration of these control genes in malignant cells favors aggressive cell proliferation. Evidence suggests that ANP therapy affects 112 genes in the GBM genome and functions as "molecular switches" which "turn on" tumor-suppressor genes and "turn off" oncogenes [27,28]. Hence, the antineoplastic action of ANP therapy in DIPG involves restoration of cell cycle control, induction of programmed cell death, and interference with cancer cell metabolism and nuclear transport.

Current sequencing technology allows for advanced understanding of the GBM genome and underlying molecular biology [29]. Identifying crucial and targetable genomic alterations can expand our therapeutic options.

Tyrosine kinase inhibitors (TKIs) have failed to demonstrate significant efficacy when targeting epidermal growth factor (EGFR) [30-32]. For persistent EGFR-amplified GMB, depatuxizumab mafodotin, an antibody drug conjugate targeting EGFR, in combination with temozolomide, has shown promising activity in a Phase II trial [33]. In contrast to this, a Phase III trial of depatuxizumab mafodotin in combination with standard therapy for newly diagnosed EGFR-amplified glioblastoma was stopped early because an interim analysis showed no OS benefit [34].

PTEN, PIK3CA, and PIK3R1 are frequently seen in IDH-wild-type GBM [35]. However, buparlisib, in persistent GBM, and everolimus

and temsirolimus, in newly-diagnosed GBM, have not shown efficacy as single agents [36-38]. Following accelerated approval to bevacizumab, trials of vascular endothelial growth factor (VEGF) and multikinase TKIs, such as cediranib, lomustine, tivozanib, pazopanib, and sunitinib have shown little or no activity as single-agent therapy [39-43].

While single-agent targeted therapy has not yet been shown to be effective in the treatment of recurrent/persistent GBM, we have published preliminary results that encourage the simultaneous use of multiple targeted agents as therapy for recurrent GBM [44]. Twenty-nine adult patients with recurrent/persistent GBM were treated at the BC between 9/11/2015 and 06/23/2018. Seven patients had no prior treatment with bevacizumab, had radiologic evidence of recurrent GBM, had MRI assessment of tumor response, and formed the study population. The treatment plan for any patient was based on genomic profiling and consisted of Antineoplaston AS2-1 and selected targeted agents for specific genomic abnormalities [45]. The median treatment time for these seven patients was 101 days (range: 55-208 days). An OR was achieved in six patients (85.7%) with a CR in four patients (57.1%) and a PR in two patients (28.6%). PD was seen in one patient (14.3%).

## Conclusion

We present here the case of a 45-year-old female with a GBM, who presented to the BC at age 46 years and eight months with recurrent/persistent GBM and obtained a cure with ANP therapy, having obtained a CR and survived 24 years since the start of ANP therapy. This therapy is an attractive option for patients with recurrent/persistent GBM who are ineligible for or refuse standard therapy or demonstrate recurrent/persistent disease following standard therapy. Multiple Phase II clinical studies of ANP therapy in a variety of low- and high-grade brain tumors under the Burzynski Research Institute's (BRI's) IND # 43,742 have now been completed and numerous articles have been published [46-85]. Based on the preliminary study cited above [44], we propose a Phase II study of AS2-1 plus targeted therapy in patients with recurrent/persistent GBM following standard of care therapy.

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