Research Article

ISSN 2771-9057

Recent Advances in Clinical Trials

Newly Diagnosed Glioblastoma: Partial Response and > 27 Years Overall Survival in 37-Year-Old Male Treated with Antineoplastons (Treatment of Glioblastoma with Antineoplastons)

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Received: 01 Nov 2022; **Accepted:** 11 Dec 2022; **Published:** 16 Dec 2022

Citation: Burzynski S, Burzynski G, Janicki T, et al. Newly Diagnosed Glioblastoma: Partial Response and > 27 Years Overall Survival in 37-Year-Old Male Treated with Antineoplastons (Treatment of Glioblastoma with Antineoplastons). Recent Adv Clin Trials. 2022; 2(2): 1-7.

ABSTRACT

Glioblastoma (GBM), with its very poor prognosis, accounts for 57% of gliomas and 48% of malignant central nervous system (CNS) tumors. After standard therapy, patients with GBM usually die within six months. The case of an adult male with a newly-diagnosed GBM is presented here to detail/discuss the efficacy of ANP therapy (Antineoplaston A10 {Atengenal} and Antineoplaston AS2-1 {Astugenal}) in the treatment of GBM and to permit a review of the Phase II Protocol BT-07. Objectives: This patient was treated at the Burzynski Clinic (BC), according to the Phase II Protocol, BT-07, which utilized IV ANP therapy in the treatment of patients with newly-diagnosed GBMs. ANP therapy was delivered via subclavian catheter and infusion pump. Tumor response was measured by sequential magnetic resonance imaging (MRI) of the brain utilizing gadolinium enhancement. Findings: At age 37, this patient was diagnosed with GBM of the right frontal lobe after subtotal tumor resection performed elsewhere. At age 37 years and six months, he presented to the BC with this newly diagnosed disease. He had a recent history of forgetfulness and personality change. Neurologic examination was otherwise normal. Baseline brain MRI at the BC revealed a measurable enhancing nodule (4.0 cm x 2.0 cm) in the right frontal lobe. Intravenous (IV) ANP therapy began in November 1995 and a partial response (PR) was achieved within three months. After another 5 months of IV ANP therapy, the patient underwent a complete tumor resection, then additional ANP therapy. Now, > 27 years later, the patient is doing well and showing no evidence of tumor recurrence. Conclusions: The utilization of ANP therapy to facilitate a cure in a patient with newly-diagnosed 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.

Keywords

Brain tumor, Glioblastoma, Recurrent glioblastoma, Newly-diagnosed glioblastoma, Phase II Studies.

Introduction

Glioblastoma (GBM) is the most common malignant central nervous system (CNS) tumor and accounts for 48% of all malignant tumors and 57% of gliomas. [1]. Exposure to ionizing radiation [2], and the Li-Fraumeni and Lynch syndromes (<1% of cases) [3] are risk factors for GBM. Negative prognostic factors include advanced age, low Karnofsky Performance Status (KPS), and less than a gross total resection at initial surgery [4,5]. 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 [6-8]. Concerning the diagnosis of GBM, the 2016 revision of the World Health Organization (WHO) of central nervous system (CNS) tumors, included IDH status, which resulted in three GBM sub-groups, IDH-wild-type, IDH-mutant, and not otherwise specified (NOS) [9,10]. IDH–wild-type GBM is characterized by de novo development with no identifiable precursor lesion and represents 90% of patients with GBM [10]. On the other hand, IDH-mutant GBM, typically arises from a

precursor diffuse or anaplastic astrocytoma and represents 10% of patients with GBM [10].

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) radiation therapy (RT) over 6 weeks with concomitant daily temozolomide followed by a further 6 cycles of maintenance temozolomide [11]. In patients with good performance status (KPS > 60), the median overall survival (OS) was 14.6 months for RT plus temozolomide vs. 12.1 months for RT alone ($P < .001$). Long term-survival is rare. The overall OS rate at five years has remained constant for two decades at 5.8% [1,12,13].

After standard therapy, most patients recur within 6 months. In this secondary 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 O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation are likely to benefit. Such methylation is seen in 30-50% of IDH-wild-type GBM [14,15]. Salvage chemotherapy with combined procarbazine, lomustine, and vincristine may have some activity, although its use is limited by significantly greater toxicity [16-19]. The quality of data for individual chemotherapy agents or regimens is generally poor and comparison of studies is difficult.

We present here the successful use of ANP therapy (Antineoplaston A10 {Atengenal} and Antineoplaston AS2-1 {Astugenal}) in the treatment of newly diagnosed GBM in a 37 year and six-month-old male, initially diagnosed at age 37 following sub-total resection of a frontal lobe tumor. We also present 1) details of protocol BT-07 and 2) the use of targeted therapy in the treatment of GBM, including our own preliminary results.

Materials and Methods

A 37-year-old attorney was in good health when he developed severe and persistent headaches accompanied by vomiting. He had a computed tomography (CT) scan of the brain performed in a local emergency room and was then referred to a neurosurgeon. Magnetic resonance imaging (MRI) of the brain revealed a right frontal lobe tumor. On October 5, 1995, the patient underwent a right frontal craniotomy with sub-total resection of the tumor. The resultant diagnosis was that of GBM. The patient refused standard treatment and elected to be treated at the Burzynski Clinic (BC). He was evaluated at the BC on November 14, 1995, where MRI of the brain showed a measurable, enhancing 4.0 cm x 2.0 cm tumor (size = 8.0 cm^2 in the right frontal lobe (Figure 1A).

During his baseline evaluation at the Burzynski Clinic (BC), the patient complained of forgetfulness and personality change. Neurologic examination was otherwise normal. Karnofsky Performance Status (KPS) was 90. On August 10, 1998, the patient began intravenous (IV) ANP therapy according to Protocol BT-07, "Phase II Study of Antineoplastons A10 and AS2-1 in Treating Patients with Newly-diagnosed Glioblastoma Multiforme." In this single arm study, IV ANP therapy was delivered every four hours via a subclavian catheter and a programmable infusion pump.

The objectives of BT-07 were to 1) determine the efficacy of ANP therapy in adults with newly diagnosed GBM as determined by an objective response (OR) to therapy; 2) determine the safety and tolerance of ANP therapy in this group of patients; and 3) determine OR utilizing MRI scans, which were performed every 8 weeks for the first two years, and then less frequently.

Eligibility criteria for BT-07 included 1) Histologically or cytologically confirmed GBM; 2) No prior therapy other than subtotal resection of tumor and/or corticosteroids for cerebral edema; 3) Tumor size ≥ 5mm; 4) Age ≥ 18 years; 5) KPS ≥ 60%; and 6) Life expectancy ≥ 4 months.

Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain was 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 were obtained. GBMs are gadolinium-enhancing, therefore sequential T1-weighted contrast-enhanced images were utilized to determine the effect of therapy [20].

As determined by MRI of the brain, the product of the two greatest perpendicular diameters of each measurable (≥ 5mm) and enhancing lesion was calculated. Tumor size was defined as the sum of these products [21,22]. The response criteria were as follows: a complete response (CR) indicated complete disappearance of all enhancing tumor while a partial response (PR) indicated a 50% or greater reduction in total measurable and enhancing tumor size. CR and PR required a confirmatory brain MRI performed at least four weeks after the initial finding. Progressive disease (PD) indicated a 25% or greater increase in total measurable and enhancing tumor size, or new measurable and enhancing disease, while stable disease (SD) did not meet the criteria for PR or PD [21].

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. This Phase II protocol is described in Clinicaltrials.gov (CDR0000066488, NCT00003456).

Results

Between March 1995 and June 2004, 40 patients were accrued to BT-07 and treated at the BC. Thirty-two patients were evaluable, while eight were not. Median age was 52.4 years (range: 26.3 to 76.2 years). Twenty-seven patients were male while thirteen were female. Two patients obtained a CR, one patient achieved a PR, two patients had SD, and 27 patients had PD.

The one patient treated according to BT-07 and obtaining a PR now has an OS of > 27 years. This patient presented with newly diagnosed disease following a subtotal resection of a right frontal lobe tumor, which provided the diagnosis of GBM. He was started on ANP therapy.

The starting dose of A10 for this patient was 1.13 g/kg/d. It was gradually increased to 10.07 g/kg d and subsequently reduced to 9.02 g/kg/d. His starting dose of AS2-1 was 0.25 g/kg/d. It was gradually increased to 0.33 g/kg/d. On February 9, 1996, after 3 months of IV ANP therapy, the patient's tumor measured 3.3 cm x 1.2 cm (size = 3.96 cm^2), a 50.5% decrease from baseline, indicating a PR. On April 8, 1996, MRI of the brain showed an 88.0% decrease from baseline, confirming the PR (Figure 1B). IV ANP therapy was discontinued after a total of 8.0 months. The patient then underwent complete resection of the residual tumor. On August 4, 1997, follow-up MRI showed no residual tumor (Figure 1C). As a compassionate exception, the patient then resumed treatment according to BT-07 and received IV ANP therapy, with A10 at 9.02 mg/kg/d and AS2-1 at 0.32 mg/kg/d, plus concomitant oral ANP therapy, with both A10 and AS2-1 at 0.25 mg/kg/d. Twenty-six days after ANP therapy re-started, the patient elected to forego any further therapy. A final MRI of the brain was performed in July 2011 and showed no signs of tumor recurrence. The patient now has an OS of >27 years since the start of IV ANP therapy and continues in excellent health and maintains a very good quality of professional life (Figure 2).

All brain MRIs showing an OR were reviewed by a prominent outside neuroradiologist. Consent was obtained from the patient for publication of the brain MRI images (Figure 1) and the photograph (Figure 2) presented in this report.

Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE v.3). Among the 40 patients accrued to BT-07, all patients experienced AEs and 18 had serious adverse events (SAE.). Only one SAE, a case of hypernatremia, was though to be due to ANP therapy and the patient fully recovered. On the other hand, the patient presented here experienced no SAEs and no adverse events thought to be due to ANP therapy.

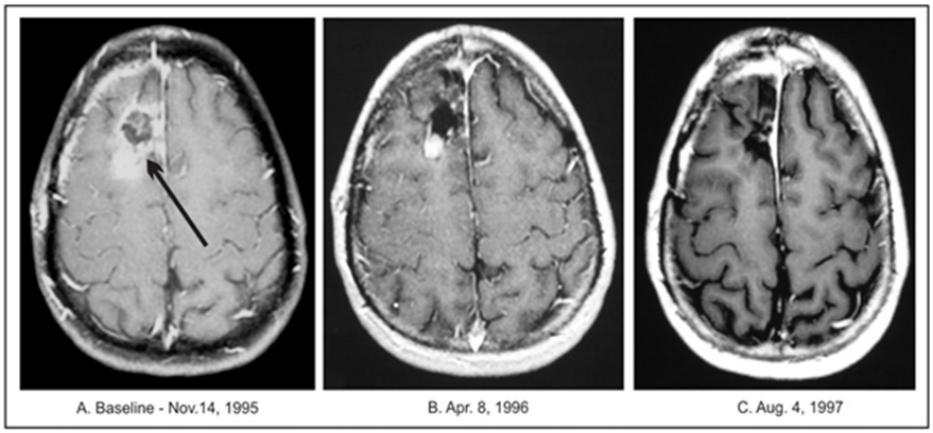

Figure 1: Axial MRI images [41]: A) Baseline MRI showing residual GBM in the right frontal lobe (arrow) following subtotal resection of GBM; B) Follow-up MRI showing an 88% reduction in the size of the residual frontal lobe GBM, confirming a PR; C) Post therapy MRI showing no residual GBM following total resection of remaining tumor.
ANP therapy: Antineoplaston A10 (Atengenal) and Antineoplaston AS2-1 (Astugenal); GBM: glioblastoma; MRI: magnetic resonance imaging; PR: Partial response.

Figure 2: Post-therapy photograph of the patient.

Discussion

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 [23]. 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-phenylacetylamino-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 phenylacetylisoglutaminate (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 [24].

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 204 mutated genes in the malignant genome and functions as a "molecular switch" which "turns on" tumor-suppressor genes and "turns off" oncogenes [25,26]. Hence, the antineoplastic action of ANP therapy in GBM involves restoration of cell cycle control, induction of programmed cell death, and interference with cancer cell metabolism and nuclear transport. In the case presented here, ANP therapy may have arrested the infiltrative growth of GBM, which is a universal characteristic of the tumor, allowing for cure with subsequent total resection.

Current sequencing technology allows for advanced understanding of the GBM genome and underlying molecular biology. Identifying crucial and targetable genomic alterations can expand our therapeutic options. Tyrosine kinase inhibitors have failed to demonstrate significant efficacy when targeting epidermal growth factor (EGFR) [27-29]. 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 [30]. 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 [31].

PTEN, PIK3CA, and PIK3R1 abnormalities are frequently seen in IDH-wild-type GBM. However, buparlisib, in persistent GBM, and everolimus and temsirolimus, in newly-diagnosed GBM, have not shown efficacy as single agents [32-33]. Trials of vascular endothelial growth factor (VEGF) and multikinase TKIs, such as cediranib, lomustine, tivozanib, pazopanib, and sunitinib have shown little or no activity [34-39].

While single agent targeted therapy has not yet been shown to be significant, we have published preliminary results that encourage the simultaneous use of AS2-1 and multiple targeted agents in the treatment of GBM [40]. Twenty-nine adult patients with recurrent GBM were treated between 9/11/2015 and 06/23/2018. Seven had no prior treatment with bevacizumab, had radiologic evidence of recurrent GBM, and had MRI assessment of tumor response. 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 [41]. The median treatment time for these seven patients was 101 days (range: 55-208 days). An OR was achieved in six patients (85.7%), a CR in four patients (57.1%), and a PR in two patients (28.6%) while PD was seen in one patient (14.3%).

Conclusions

We have presented here the case of a 37-year-old male with a newly-diagnosed GBM who obtained a PR with ANP therapy and then was cured with subsequent surgery. ANP therapy is an attractive option for patients with newly-diagnosed GBM who are ineligible for or refuse 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 [42-79]. Based on the preliminary results cited above, we propose a Phase II study of AS2-1 pus targeted therapy in patients with GBM.

Acknowledgements

The authors express their appreciation to Carolyn Powers for preparation of the manuscript and to Ramiro Rivera, Mohamed Khan, Jennifer Pineda and Adam Golunski for their involvement.

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