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Progressive, Multicentric, Midline, Low-grade Glioma: Survival Greater Than 24.8 Years in Three Patients Treated with Antineoplastons A10 and AS2-1 in Phase II Studies

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Abstract

Background: *Midline low-grade gliomas occur in children and young adults, impinging on critical areas of the brain, significantly impacting quality of life, and presenting difficult therapeutic challenges.*

Problem: *The morbidity of surgery, chemotherapy, and radiotherapy has been life-altering. We address the utility of Antineoplaston therapy in this context.*

Methods: *Three patients with midline, low-grade gliomas are presented, all being treated at the Burzynski Clinic, under IND 43,742, in single arm, two stage, Phase 2 protocols utilizing Antineoplastons. Dosages and duration of treatment with IV Antineoplastons A10 and AS2-1, were according to protocol, with doses being delivered via programmable pump and subclavian catheter. Oral A10 and AS2-1 were also utilized. Sequential brain MRIs were used to determine response to therapy. No patient received anti-cancer treatment before or after receiving Antineoplastons.*

Findings: *Patient, histological, treatment, adverse events, and survival data are presented below. One patient achieved a partial response with Antineoplaston therapy while two achieved complete responses. These patients have survived >24.8 years, >25.2 years, and >27.6 years from the start of Antineoplastons therapy. All symptoms and signs, including paresis, ataxia, and cranial nerve dysfunction, had cleared at last follow-up. Adverse events and serious adverse events were reversable in all instances.*

Summary: *Antineoplastons produced objective responses in the three patients presented here, all of whom are alive and well after long-term survival. As such, Antineoplastons are reasonable therapy for patients with midline, low-grade gliomas. We propose a multicentric Phase 2 study of midline low-grade glioma, utilizing Antineoplastons, in follow-up to these findings.*

Result: *Three patients with progressive, multicentric, midline low-grade glioma was treated with Antineoplastons and developed objective responses, one partial response and two complete responses, all of which have persisted for greater than 24.8 years.*

Conclusion: *Antineoplastons are reasonable therapy for patients with otherwise uncurable midline low-grade gliomas.*

Keywords: *Antineoplastons; Midline Low-grade Glioma; Multicentric Midline Low-grade Glioma; Progressive Multicentric Midline Low-grade Glioma; Phase 2 Clinical Trials.*

1. Introduction

Gliomas consist of a variety of tumors originating from the supporting glial cells of the central nervous system (CNS) and include astrocytomas. Based upon histopathological characteristics, the World Health Organization (WHO) classification system categorizes gliomas from grade 1 (lowest grade) through grade 4 (highest grade). Low-grade gliomas (LGGs) consist of grade 1 and 2 tumors, with grade 2 tumors exhibiting cytologic atypia [1]. Low-grade midline gliomas are a subset of gliomas that frequently occur in children and young adults and account for a small percentage of all brain tumors. They are usually located in the brainstem, thalamus, and spinal cord [2]. Their location in critical areas of the brain may significantly impact a patient's quality of life and make treatment challenging [2]. Their etiology is not well understood, but specific *genetic mutations*, i.e., alterations in the *MAPK pathway*, may be involved in their development [2].

Low-grade midline tumors produce symptoms and signs related to their location, including cranial neuropathies, ataxia, long tract signs, and hydrocephalus [3,4]. Others may present with cognitive or behavioral changes, or focal neurologic deficits. Some patients may be asymptomatic.

Magnetic resonance imaging (MRI) of the brain is the preferred imaging modality. LGGs often show low signal intensity on T1-weighted sequences and hyperintensity on T2-weighted and Fluid-Attenuated Inversion Recovery (FLAIR) sequences [5]. Calcifications may be evident in up to 20% of lesions, including astrocytomas, and are particularly suggestive of oligodendrogliomas [5]. Contrast enhancement, while usually minimal, can be seen in up to 60% of LGG [4].

The primary objective of initial surgery is to obtain tissue for a histopathological diagnosis. Intraoperative neurophysiological monitoring allows for maximal resection of T2/FLAIR abnormalities on brain MRI [4]. When surgical resection is not safe, tumors can undergo stereotactic biopsy using preoperative or intraoperative MRI imaging to obtain tissue for histopathological analysis. Components of the tumor with potentially higher grade, i.e., contrast enhancement, are selected for biopsy. Even so, biopsy may not reflect the highest grade for diagnosis, with reported accuracy rates ranging from 51% to 83% [4]. Once obtained, the tissue sample is stained using hematoxylin and eosin, which allows for identification and classification of tumor type. Astrocytomas demonstrate fibrillary neoplastic astrocytes on a loose tumor matrix background. As mentioned above, grade 2 tumors will show cytologic atypia [1].

Genetic characterization has recently become important in tumor classification and can be predictive of tumor behavior, including prognosis +/- response to treatment. Deletion of selected regions on *chromosomes 1p and 19q* is important in low-grade gliomas, as it is associated with the oligodendroglioma tumor subtype [6]. Loss of the *1p36 region* has been noted in 18% of astrocytomas and 73% of oligodendrogliomas; loss of the *19q13.3 region* is described in 38% of astrocytomas and 73% of oligodendrogliomas, while *the 1p36 and 19q13.3 regions* are codeleted in 11% of astrocytomas and 64% of oligodendrogliomas [6]. *Isocitrate dehydrogenase 1 and 2 gene mutations* (*IDH1* and *IDH2*) have been reported in LGGs [7]. In addition, *mutation and overexpression of tumor protein 53* (*TP53*) are said to be *genetic markers* for low-grade astrocytoma [8]. In distinguishing between gliosis and tumor, the presence of *TP53* and *IDH1 expression* can establish the diagnosis of tumor [8]. *IDH1 and IDH2 gene mutations* have been associated with prolonged survival and enhanced sensitivity to the oral alkylating agent temozolomide [9].

In addition to the above, immunohistochemical labeling of antibodies against the *Ki-67 nuclear proliferation-related protein (Ki-67, MIB-1)* is used to evaluate the mitotic activity of glioma cells. In LGG, these indices are generally low (<6%), suggesting low mitotic activity [10].

While gross total resection (GTR), when possible, is the optimal treatment for LGG, there is no standard therapeutic approach to progressive, multicentric, midline LGG. The morbidity of repeat surgery, chemotherapy, and radiotherapy (RT) is life-altering.

2. Material and Methods

Antineoplaston research began in 1967, when significant deficiencies were noticed in the peptide content of the serum of patients with cancer compared with healthy people. Initially Antineoplastons were isolated from the blood and later from urine [11]. Subsequent studies of the isolated Antineoplastons demonstrated that Antineoplaston A10 and Antineoplaston AS2-1 were the most active Antineoplastons. The chemical name of Antineoplaston A10 is 3-phenylacetylamino-2,6-piperidinedione. It consists of the cyclic form of L-glutamine connected by a peptide bond to a 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 an 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 [12].

We address here the utility of Antineoplastons in the context of three patients with progressive, multicentric, midline, LGG seen at the BC, between 1996 and 1999, for assessment and treatment of their LGGs. One female child was treated according to Protocol BT-13, "A Phase II Study of Antineoplastons A10 and AS2-1 in Children with Low Grade Astrocytomas" [13] while one male child and one male adult were treated according to Protocol BT-11, "A Phase II Study of Antineoplastons A10 and AS2-1 In Patients with Brain Stem Glioma [14]. Both Protocols were single arm, two-stage, phase II trials of Antineoplaston therapy of patients with radiologic evidence of an "uncurable" brain tumor. In both protocols, IV Antineoplastons were utilized first with the possibility of subsequent oral Antineoplastons once an OR was achieved. Patients received gradually increasing doses of IV A10 and IV AS2-1 via subclavian catheter and infusion pump, until a maximum tolerated dose of each component was achieved. Eligibility criteria included a Lansky/Karnofsky score of 60-100%, and a life expectancy of > 2 months. All study patients and/or their legal guardians read, understood, and signed an Informed Consent Document prior to treatment. Outcome criteria were 1) objective response (OR) and 2) overall survival from the start of Antineoplaston therapy (OSS). The safety and tolerance of Antineoplastons in patients with brain tumors were also investigated. Disease progression, unacceptable toxicity, physician decision, or patient request resulted in termination of Antineoplaston therapy.

Gadolinium-enhanced MRIs of the brain were used in the diagnosis and follow-up of these three patient's LGGs. Brain MRIs were performed every 8 weeks for the first two years and then less frequently. T2-weighted, T2-FLAIR, T1 weighted, and T1-weighted contrast-enhanced images were obtained. LGGs exhibit gadolinium-enhancing and sequential T1-weighted contrast-enhanced images were utilized to determine the effect of therapy. [15] 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 [15,16]. 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 [15].The Phase II trials were 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.

3. Results

Child #1, a nine-year and two-month-old white female, developed a tremor of her right hand and leg in the summer of 1996. Brain MRI showed a tumor in the left thalamus that extended to the upper brainstem. The child underwent left-sided craniotomy and partial resection of the thalamic mass at the University of Virginia Health Sciences Center, Charlotteville, VA on September 20, 1996. The histopathological diagnosis was astrocytoma, grade 2. The child received no other treatment as her parents refused the offered chemotherapy and RT. When symptoms worsened, the child was evaluated at the BC. On physical examination, she showed right-sided ataxia and weakness with footdrop. She was admitted to Protocol BT-13, "A Phase II Study of Antineoplastons A10 and AS2-1 in the Treatment of Children with Low-grade Astrocytoma". Baseline MRI of the brain (November 8, 1996) showed PD with seven enhancing lesions and a SUM of 10.06 cm^2 (Figure 1). IV Antineoplaston therapy was initiated on November 26, 1996 and by March 5, 1997, A10 had been gradually increased to 9.01 g/kg/day and then reduced to 7.94 g/kg/d, while AS2-1 had been gradually increased to 0.41 g/kg/d and then reduced to 0.33 g/kg/d. Brain MRI performed on March 5, 1997, showed a SUM of 4.84 (decrease of 51.9%) indicating achievement of a PR. Sequential MRIs showed further decreases in SUM and greater percent decreases from baseline. On September 26, 1977, the SUM was 2.59 cm^2 (decrease of 74.3%). Brain MRI on November 6, 1997, showed a SUM of 5.22 cm^2, which was an increase of 101.5% from that seen on September 26, 1977, indicating PD. However, sequential MRIs then showed decreases in SUM and greater percent decreases from baseline. On March 9, 1998, brain MRI showed a SUM of 2.36 cm^2 (76.5% decrease from baseline – see Figure 1). A brain MRI performed October 2, 2017, showed long-term persistence of the PR (Figure 1). IV Antineoplaston therapy was discontinued on June 12, 1999, and the child was placed on oral Antineoplaston therapy from July 12, 1999, until November 8, 1999. Based on correspondence dated September 14, 2021, overall survival since the start of Antineoplastons (OSS) was 24.8 years and all signs and symptoms had cleared. During her course of therapy, this child developed no Serious Adverse Events (SAEs) and fully recovered fully from all AEs (Table 1).

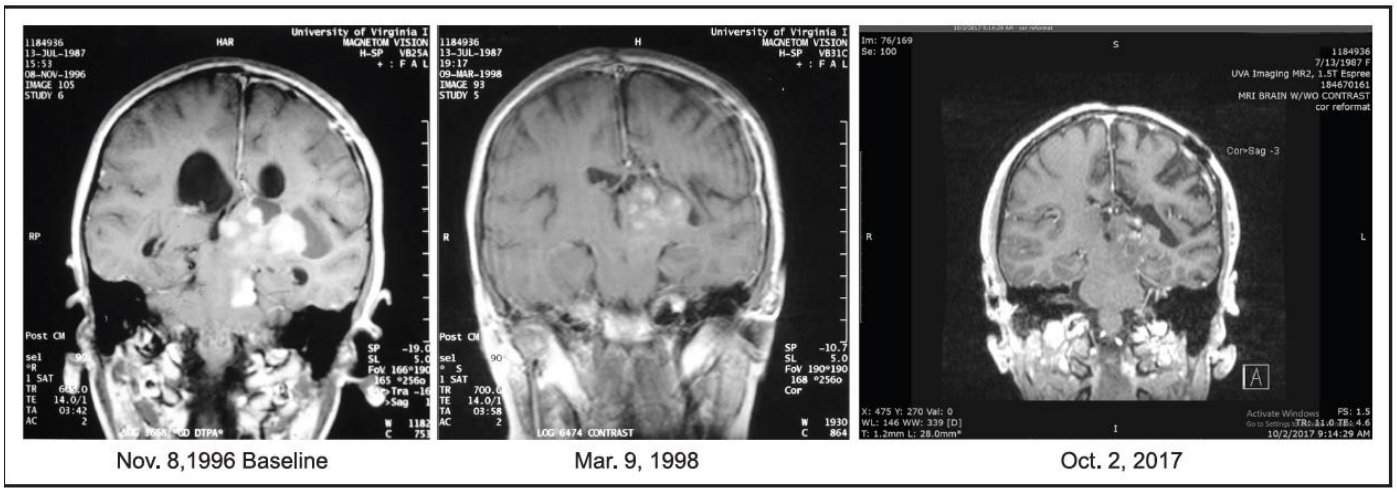

Figure 1: Brain MRIs (T1-weighted, axial views), Child #1: **November 8, 1966:** Baseline MRI of the brain showing seven enhancing lesions with a SUM of 10.06 cm^2; **March 9, 1966:** Brain MRI showing a SUM of 2.24 cm^2 (76.5% decrease from baseline), indicating achievement of a PR; **October 2, 2017:** The last brain MRI completed showed long-term persistence of the PR. **MRI:** Magnetic resonance imaging; **PR:** Partial response; **SUM:** the sum of the products of the two greatest perpendicular diameters of each measurable (≥ 5mm) and enhancing lesion.

Child #2, a 12-year and 11-month-old white male, developed left-sided weakness and ataxia in November 1998. These problems worsened and a brain MRI performed on May 27, 1999, showed a tumor in the thalamus, hypothalamus, midbrain and pons. The child underwent stereotactic biopsy of the tumor on June 15, 1999, at the Artmouth-Hitchcock Medical Center, Lebanon, NH, with a histopathological diagnosis of astrocytoma, grade 2. The child received no other treatment and, when symptoms worsened, he was evaluated at the BC. On physical examination, the child showed left-sided hemiparesis (Babinski positive) and was unable to stand and walk unassisted. There was ataxia of the right hand and complaints of dizziness. He was admitted to Protocol BT-11, "A Phase II Study of Antineoplastons A10

and AS2-1 in Patients with Brain Stem Glioma". Baseline MRI of the brain (July 19, 1999) showed PD with two enhancing lesions and a SUM of 12.80 cm^2 (Figure 2).

IV Antineoplaston therapy was initiated on July 23, 1999, and by November 8, 1999, A10 had been gradually increased to 9.11 g/kg/day and then reduced to 6.20 g/kg/d, while AS2-1 had been gradually increased to 0.45 g/kg/d and then reduced to 0.14 g/kg/d. Brain MRI performed on November 8, 1999, indicated achievement of a CR. IV Antineoplaston therapy was stopped on June 19, 2000, and oral Antineoplaston therapy was started the same day. However, follow-up brain MRI on October 30, 2000, showed growth of enhancing disease with a SUM of 3.34 cm^2 (73.9% of the baseline SUM), indicating PD. Oral Antineoplaston therapy was stopped on November 10, 2000, and IV Antineoplaston therapy was resumed on November 11, 2000. By July 12, 2002, A10 had been gradually increased to 10.31 g/k/day and then reduced to 7.82 g/kg/d, while AS2-1 had been gradually increased to 0.34 g/kg/d and then reduced to 0.26 g/kg/d. On July 12, 2002, brain MRI showed persistent enhancing disease with a SUM of 4.86 cm^2 (62% decrease from baseline). On August 16, 2002, IV Antineoplaston therapy was stopped and oral Antineoplaston therapy was resumed on August 30, 2002. It was continued until April 2, 2005. Follow-up brain MRI, performed on June 2, 2003, again indicated achievement of a CR (Figure 2). Thereafter, repeated brain MRIs, the last being July 19, 2007 (Figure 2), showed long-term persistence of the CR. Based on correspondence dated October 18, 2024, OSS was 25.2 years, and all signs and symptoms had cleared. During his course of therapy, this child developed five Serious Adverse Events (SAEs), none of which were related to Antineoplaston, and recovered fully from them all (Table 1).

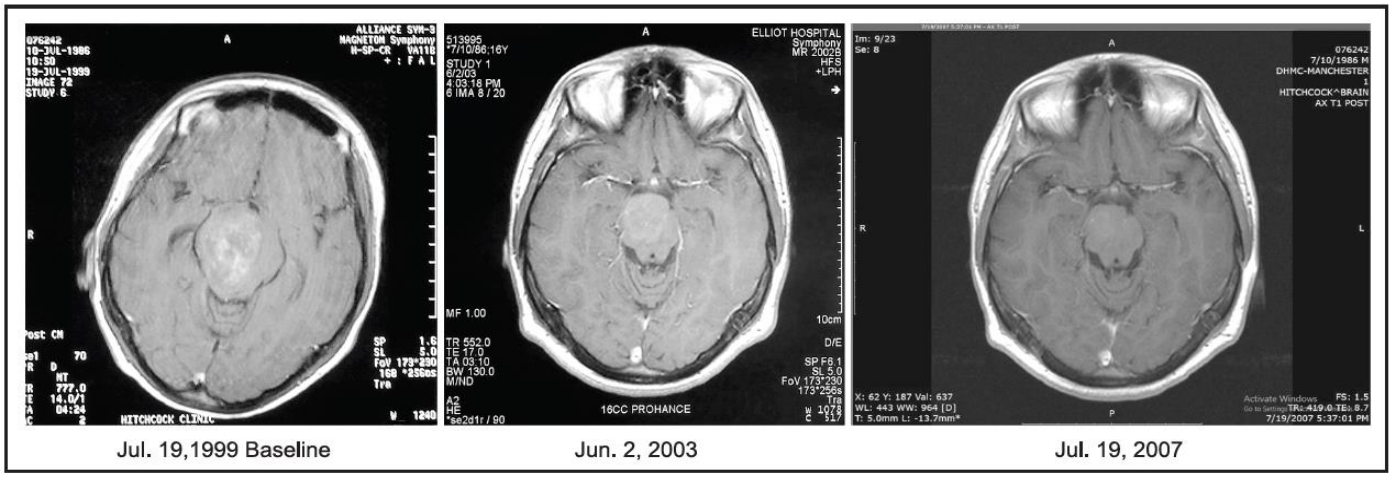

Figure 2: Brain MRIs (T1-weighted, axial views), Child #2: **July 19, 1999:** Baseline MRI of the brain showing two enhancing lesions with a SUM of 12.80 cm^2; **June 2, 2003:** Brain MRI showing no enhancing lesions, indicating achievement of a CR; **July 19, 2007:** The last brain MRI completed showed long-term persistence of the CR.
CR: Complete response; **MRI:** Magnetic resonance imaging; **SUM:** the sum of the products of the two greatest perpendicular diameters of each measurable (≥ 5mm) and enhancing lesion.

Adult #1, a 29-year and 8-months-old white male, developed diplopia in August 1996 and tinnitus with "numbness" of both arms in October 1996. A brain MRI performed at the Steinberg Diagnostic Medical Imaging Center, Las Vegas, NV on February 20, 1997, showed two enhancing brain stem tumors, but two attempts at stereotactic biopsy were unsuccessful. The patient received no other treatment and was subsequently evaluated at the BC. On physical examination, both pupils were dilated with the left pupil being dilated more than the right pupil. The left pupil did not respond to light while there was a decrease in the right pupil's response to light. The patient complained of fatigue, headaches, dizziness, and numbness in his arms. He was admitted to Protocol BT-11, "A Phase II Study of Antineoplastons A10 and AS2-1 in Patients with Brain Stem Glioma". Baseline MRI of the brain (March 11, 1997) showed PD with two enhancing lesions and a SUM of 1.30 cm^2 (Figure 3). IV Antineoplaston therapy was initiated on March 13, 1997, and by November 18, 1997, had been gradually increased to 10.55 g/kg/day and then reduced to 10.07 g/kg/d, while AS2-1 had been gradually increased to 0.34 g/kg/d and then reduced to 0.33 g/kg/d. Brain MRI performed on November 18, 1997, indicated achievement of a CR. IV Antineoplaston therapy was stopped on July 21, 1998, and oral Antineoplaston therapy was started on July 24, 1998. However, follow-up brain MRIs on December 11, 1998, and January 29, 1998, showed enhancing disease with a SUM of 0.12 cm^2 (90.8% of the baseline SUM), indicating PD. Oral Antineoplaston therapy was stopped on December 11, 1998, and IV Antineoplaston was resumed on December 12, 1998. By May 5, 1999, A10 had gradually reached a dosage of 9.56 g/kg/d, while AS2-1 had gradually reached a dosage of 0.31 g/kg/d. Brain MRI performed that day again indicated achievement of a CR (Figure 3). Thereafter, repeated brain MRIs, the last being on January 24, 2000 (Figure 3), showed long-term persistence of the CR. IV Antineoplaston therapy was discontinued on February 13, 2000, and the patient was placed on oral Antineoplaston therapy from March 1, 2000, until March 10, 2000, when the patient declined further therapy. Based on correspondence dated October 18, 2024, OSS was 27.6 years, and all signs and symptoms had cleared. During his course of therapy, this patient developed two SAEs, both of which were unrelated to Antineoplaston, and recovered fully from them both and from all AEs (Table 1).

4. Discussion

There is little information available in the published literature concerning the treatment of multicentric, midline, LGG. Even for the treatment of LGG, there are significant challenges in the design of clinical trials including: 1) distin-guishing between the multiple histological sub-types of LGG and the growing number of molecular sub-types; 2) a lack of consensus regarding the appropriate use of RT; and 3) a paucity of knowledge concerning chemotherapy [3].

Pouratian and colleagues conducted a comprehensive review of the surgical management of LGG [4]. Nine retrospective surgical studies were reviewed, six of which demonstrated improved survival with extensive resection. Two prospective studies of surgery plus radiation therapy (RT) demonstrated improved survival with extensive resection on univariate analysis [4]. In another comprehensive review, Sanai and colleagues analyzed ten studies of the effect of extent of surgical resection on glioma outcome [17]. By univariate and multivariate analysis, they determined that the extent of surgery did significantly impact survival in seven of the ten studies. None of the studies analyzed had performed a sub-group analysis of multicentric, midline LGG. "Curative" surgery is rarely possible in this group of patients.

Table 1: Patient, Tumor, Treatment, Serious Adverse Event, and Survival Data.

Case	Gender	Age at first diagnosis	Surgery or biopsy	Histopatho--logical (WHO) or clinical diagnosis	Other Treatment	Age at first BC visit	Symptoms and signs upon first evaluation at BC	Treated according to Protocol	Days of IV ANP therapy	Days of Oral ANP therapy	Best response to ANP therapy	Serious Adverse Events (SAEs) and outcome	Overall survival from the start of ANP therapy (OSS)	Status of Signs and Symptoms at last follow-up
Child #1	Female	9 years and 2 months	Surgery	Astrocytoma, grade 2	None	9 years and 4 months	Right-sided ataxia and weakness with footdrop	BT-13	820	118	PR	None	>24.8 years	All resolved
Child #2	Male	12 years and 11 months	Biopsy	Astrocytoma, grade 2	None	13 years	Left-sided hemiparesis, Babinski positive, unable to stand/walk unassisted, ataxia of the right hand, and complaints of dizziness	BT-11	908	1089	CR	Five, all resolved	>25.2 years	All resolved
Adult #1	Male	29 years and 5 months	Two failed biopsy attempts	Glioma	None	29 years and 8 months	Pupils dilated (L>R), left pupil unresponsive to light, decreased responsiveness of the right pupil to light, complaints of fatigue, headaches, dizziness, and numbness of arms	BT-11	880	594	CR	Two, both resolved	>27.6 years	All resolved

ANP=Antineoplaston; BC=Burzynski Clinic; CR=Complete Response; IV=Intravenous; PR=Partial Response; WHO=World Health Organization.

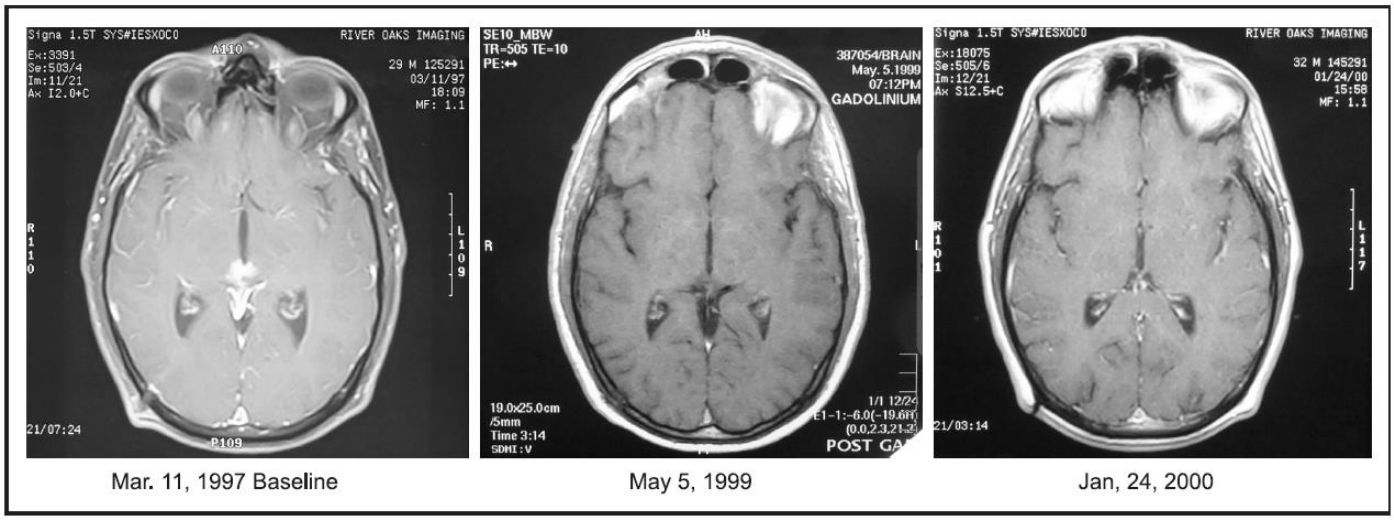

Figure 3: Brain MRIs (T1-weighted, axial views), Child #3: **March 11, 1997:** Baseline MRI of the brain showing two enhancing lesions with a SUM of 1.30 cm^2; **May 5, 1999:** Brain MRI showing no enhancing lesions, indicating achievement of a CR; **January 24, 2000:** The last brain MRI completed showed long-term persistence of the CR.
CR: Complete response; **MRI:** Magnetic resonance imaging; **SUM:** the sum of the products of the two greatest perpendicular diameters of each measurable (≥ 5mm) and enhancing lesion.

RT is frequently used as adjuvant therapy for LGG. To determine the prognostic value of high dose versus low dose RT, 379 patients with LGG were randomized to receive RT post-operatively or post biopsy [18]. One cohort received 45 Gray (Gy) over 5 weeks while the other received 59.4 Gy in 6.6 weeks. With a median follow-up of 74 months, no difference in survival was seen. Similar results have been observed in other large, randomized studies [19]. None of these studies performed sub-group analyses for multicentric, midline LGGs. The adverse effects of RT on midline structures are well known. Regarding chemotherapy, *IDH1* and *IDH2* gene *mutations* have been associated with prolonged survival and enhanced sensitivity to the oral alkylating agent temozolomide [9].

The mechanism of action of Antineoplastons 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 Antineoplaston affects more than *400 mutated genes* in the *malignant genome* and functions as a "molecular switch" which "turns on" *tumor-suppressor genes* and "turns off" *oncogenes* [21, 22]. Hence, the antineoplastic action of Antineoplaston involves restoration of cell cycle control, induction of programmed cell death, and interference with cancer cell metabolism and nuclear transport.

OSS of more than 24.8 years has been observed in all the patients presented here, which highlights the importance of OSS as a study endpoint in clinical studies of Antineoplaston therapy. Other significant observations include the achievement of an OR and subsequent PD following dosage reduction (Child #1) or cessation of IV Antineoplastons (Child #2; Adult #1). With higher doses of IV Antineoplastons (Child #1) a PR was again seen. With establishment of oral Antineoplaston therapy (Child #2) or re-establishment of IV Antineoplaston therapy (Adult #1), CRs were again seen. This replication of the effectiveness of Antineoplaston therapy based on dosage and/or type of administration enhances Antineoplaston therapy's validity as an appropriate treatment for progressive multicentric, midline LGGs.

5. Conclusions

We present here the use of Antineoplaston therapy in the treatment of progressive, multicentric, midline LGG in two children and one adult. All achieved ORs (one PR and two CRs) with OSS of >24.8, >25.2, and >27.6 years. In the absence of standardized treatment regimens for such patients, the use of Antineoplaston therapy avoids the negative sequalae of chemotherapy, RT, and/or surgery. Antineoplaston therapy has proved to be an attractive option for a wide spectrum of patients with persistent, recurrent, disseminated, and/or metastatic brain tumors. Multiple Phase II clinical studies of Antineoplaston therapy in a variety of low-and high-grade brain tumors, under the Burzynski Research Institute's IND # 43,742, have now been completed and numerous articles have been published [23-68]. Based on our findings, we propose a multi-institutional Phase II clinical study of Antineoplaston therapy in midline LGG.

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Authors contribution: All authors have contributed to this report and agree with its contents, conclusions, and publication.

Approval statement from Patient: Patients signed an "Authorization for Release of Protected Health Information (PHI)" on the following dates: 8/30/2023 (child #1), 1/4/2013 (child #2) and 1/26/2015 (adult #1). Copies of these authorizations are on file and available for review as necessary.

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