

Twenty-Two Year Survival in 15-Year-Old Female with a Recurrent Posterior Fossa Ependymoma Treated with Antineoplastons

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ABSTRACT

Purpose: Posterior fossa Ependymoma typically arise in the floor of the fourth ventricle and can extend through the foramen of Luschka or foramen of Magendie causing hydrocephalus. They can present with headache, double vision, cranial nerve dysfunction, and torticollis. Treatment normally consists of surgery and radiation therapy (RT). This original article discusses the use of intravenous (IV) and oral Antineoplastons A10 and AS2-1 (ANP therapy) in the treatment of a 15-year-old female with a recurrent posterior fossa ependymoma.

Material and Methods: This African-American female was first seen at the Burzynski Clinic (BC) on January 21, 1997, four years following completion of subtotal resection, RT, and chemotherapy elsewhere. MRI of the brain showed a 13.3 cm² enhancing posterior fossa mass on coronal images. Physical exam demonstrated hearing loss in the right ear and a well-healed suboccipital scar. Lansky score was 90%. The patient was enrolled in BT-24, a Phase II protocol utilizing ANP therapy in the treatment of ependymomas.

Results: Tumor response to ANP therapy was measured utilizing sequential magnetic resonance images (MRIs) of the brain, with and without gadolinium contrast. Following 2.5 years of IV and oral ANP therapy, a partial response (PR) was obtained. There has been no evidence of tumor progression now for 22 years.

Conclusions: ANP is an effective treatment for some posterior fossa ependymomas and for a variety of other low- and high-grade brain tumors. Multiple Phase II protocols utilizing ANP have now been completed and its impact on the treatment of brain tumors has been widely published.

Keywords: Brain tumor, Ependymoma, Posterior fossa ependymoma, Recurrent posterior fossa ependymoma, IV Antineoplastic therapy, Oral Antineoplastic therapy, Phase II clinical study

Abbreviations: A10: Antineoplastic A10; AS2-1: Antineoplastic AS2-1; ANP Therapy: Antineoplastons A10 and AS2-1 (IV and oral); Atengenal: Antineoplastic A10; Astugenal: Antineoplastic AS2-1; CR: Complete Response; CT: Computed Tomography; BC: Burzynski Clinic; BRI: Burzynski Research Institute; FLAIR: Fluid-Attenuated Inversion Recovery; isoPG: Phenylacetylglutamine; IV: Intravenous; MRI: Magnetic Resonance Imaging; OR: Objective Response; PD: Progressive Disease; PG: Phenylacetylglutamine; PN: Phenylacetate; PR: Partial Response; RT: Radiation Therapy; SCE: Spinal Cord Ependymoma; SD: Stable Disease; WHO: World Health Organization

INTRODUCTION

Ependymomas are rare glial tumors that account for approximately 7% of all intracranial neoplasms in adults [1]. However, ependymomas are among the most common brain tumors in children. More than half of these cases occur in children under the age of five [2]. They are most commonly found within the posterior fossa (60%), followed by the supratentorial region (30%) and spinal canal (10%) [3]. The World Health Organization (WHO) classification system of ependymomas ranges from WHO Grade I-III depending on the location and histologic appearance [1]. Ependymomas in the adult population

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typically, present when they are larger than 4 cm² in size and often contain cystic components, whereas ependymomas in the pediatric population are usually solid and smaller in size at presentation [4].

Intracranial ependymomas are most commonly WHO Grade II and occur in both children and adults. Infratentorial ependymomas most often arise in children as posterior fossa tumors [4] while supratentorial ependymomas are typically seen in younger to middle age adults [5]. The MRI features of ependymomas include low T1, high T2, and iso- to high fluid-attenuated inversion recovery (FLAIR) signal intensity due to their increased myxoid component [6]. Ependymomas are heterogeneously enhancing masses that demonstrate avid enhancement of the soft tissue components with adjacent areas of little to no enhancement. Anaplastic ependymoma, which is typically supratentorial, is a WHO Grade III intracranial tumor that is more aggressive with a higher proliferative rate and a greater tendency for infiltration and dissemination into the cerebrospinal fluid [7]. It is a rare tumor and its criteria for histopathologic grading is not well established, but includes marked hypercellularity, nuclear atypia, and increased mitotic activity. Supratentorial ependymoma can present with headache, weakness, visual field loss, and seizures.

In the posterior fossa, ependymomas typically arise in the floor of the fourth ventricle and the infiltrative nature of these tumors can result in extension from the fourth ventricle through the foramen of Luschka or foramen of Magendie [8]. Posterior fossa ependymoma can present with headache, double vision, other cranial nerve dysfunction, and torticollis (turning the head to one side).

Spinal cord ependymoma (SCE) is a rare tumor that is most commonly low-grade. Complete surgical resection has been established as first-line treatment and can be curative. However, SCEs tend to recur when complete tumor resection is not possible. Evidence supporting the use of adjuvant radiation and chemotherapy is not definitive [9]. Spinal cord ependymoma may present with weakness and/or loss of sensation, pain, and bowel or bladder dysfunction. Primary therapy for ependymomas is surgery with or without radiation therapy (RT). In a follow-up study of 101 cases, the postoperative prognosis was poor in intracranial tumors. RT increased the survival time but was not curative. The prognosis in patients with spinal ependymomas was much better, with 75% of the patients surviving for at least 10 years. Anaplastic histology has been associated with a poor prognosis [10].

We present here the case of an African-American female with a recurrent posterior fossa ependymoma who, after surgery, RT and chemotherapy elsewhere, presented to the Burzynski Clinic (BC) when she was 15 years of age.

METHODS

In 1992, a 10-year-old female presented to her pediatrician because of headaches, dizziness, and blurred vision. In February of 1992, Computed tomography (CT) scan of the brain demonstrated a large mass extending from the fourth ventricle into the foramina of Lushka and Magendie with accompanying obstructive hydrocephalus. On February 17, 1992, 90-95% of the tumor was removed via a suboccipital craniotomy. Histologic examination of the surgical specimen revealed an ependymoma. Post-operative magnetic resonance imaging (MRI) of the brain, with and without gadolinium contrast, revealed a small residual enhancing lesion in the posterior fossa with associated enhancement of the meninges. From April 7, 1992 through May 20, 1992, 5400 cGy RT was given to the fourth ventricle and the upper cervical spine. MRI performed on June 11, 1992 showed a reduction in the enhancement previously seen. From June 29, 1992 through February 13, 1993, the patient received chemotherapy (Vincristine, Carboplatin, VP-16, Ifosfamide, and Mesna). On January 13, 1993, MRI showed post-operative changes, a decrease in the size of the ventricles, and no residual enhancement. However, on January 3, 1997 (4 years later), MRI of the brain and spine showed a recurrent tumor in the prepontine space and suprasellar area with extension across the midline.

The patient was seen at the Burzynski Clinic (BC) on January 21, 1997. She was a 15-year-old African-American high school student. Physical exam revealed hearing loss in the right ear and a well-healed suboccipital scar. Lansky score was 90%. MRI of the brain performed on the same day showed a 13.3 cm² enhancing posterior fossa tumor on coronal images (**Figure 1**). On January 23, 1997, the patient was enrolled in BT-24, a "Phase II Study of Antineoplastons A10 and AS2-1 (ANP therapy) In Patients with Ependymomas". This was a single arm, open label study in which patients with persistent, progressive, or recurrent ependymoma received gradually increasing doses of intravenous (IV) A10 and IV AS2-1 via subclavian catheter and infusion pump, until a maximum tolerated dose of each component was achieved. When an objective response (OR) was achieved, ANP therapy (IV or oral) was continued 6 to 12 months. Disease progression, unacceptable toxicity, physician decision, or patient request resulted in termination of ANP therapy.

The eligibility criteria for BT-24 included age > 6 months, histologically confirmed ependymoma, baseline MRI of the brain demonstrating a persistent, progressive, or recurrent ependymoma, which was ≥ 5 mm in size, Lansky/Karnofsky score of 60-100%, and life expectancy of > 2 months. All study subjects or their guardians read, understood, and signed a written informed consent prior to enrollment. Outcome criteria were 1) OR and 2) survival. The safety and tolerance of ANP therapy in patients with ependymomas were also investigated.

To determine OR, tumor size was measured utilizing sequential MRIs of the brain, with and without gadolinium enhancement. Tumor size was calculated as the product of the two greatest perpendicular diameters as determined by imaging. Response criteria were as follows: a complete response (CR) indicated complete disappearance of all enhancing tumor while a partial response (PR) indicated a $\geq$

50% reduction in enhancing tumor size. CR and PR required a confirmatory MRI performed at least four weeks after the initial finding. Progressive disease (PD) indicated a $\geq 25\%$ increase in enhancing tumor size, or new enhancing disease, while stable disease (SD) did not meet the criteria for PR or PD [11]. All MRIs were reviewed by a prominent outside radiologist.

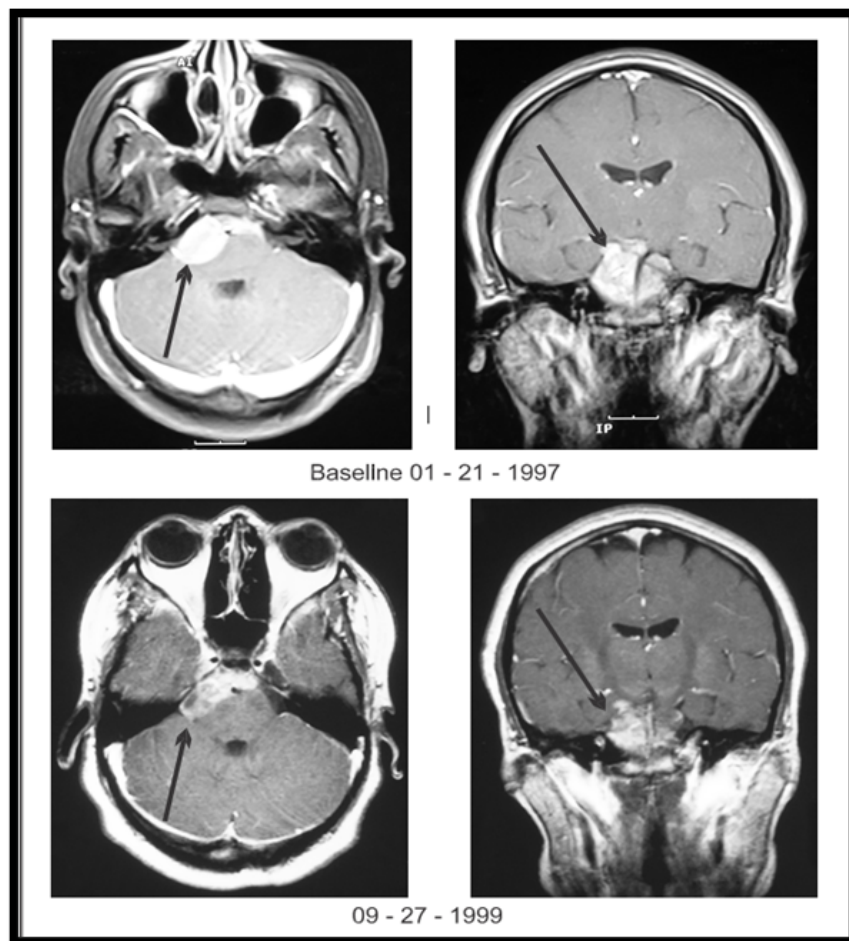


Figure 1. T1 weighted images (axial images on the left; coronal images on the right).

Baseline MRI performed at the BC (January 21, 1997) shows a 13.30 cm^2 enhancing tumor in the posterior fossa on coronal imaging. The enhancing tumor is also demonstrated in the axial images (see corresponding arrows). MRI performed at the BC (September 9, 1999) shows a 6.40 cm^2 enhancing tumor in the same location on coronal imaging. This 51.9% reduction in volume indicated a PR to ANP therapy. MRI: Magnetic Resonance Imaging; BC: Burzynski Clinic; PR: Partial Response; ANP Therapy: Antineoplaston A10 and AS2-1 (IV and oral)

RESULTS AND DISCUSSION

BT-24 began accruing patients in July 1966 and was closed in October 2000 due to slow accrual of patients. Nine patients, in total, were accrued, of which 5 (55.6%) were female. All study subjects were seen at the BC. The median age was 7.3 years (range of 1.6 to 35.7 years). Three patients were not evaluable. Of the six evaluable patients, one patient (presented here) had a PR, two patients had SD, and 3 patients had PD. All evaluable patients survived at least 6 months; four patients survived at least 12 months; three

patients survived at least 24 months; two patients survived at least 48 months; and one patient survived more than 60 months.

As previously discussed, the patient presented here achieved a PR on ANP therapy and has experienced long-term survival. Baseline MRI (January 21, 1997) showed an enhancing lesion measuring 13.30 cm^2 on coronal images (**Figure 1**). The patient was treated with IV ANP therapy per BT-24. The dosages of A10 and AS2-1 were gradually increased to 16.21 g/kg/d and 0.43 g/kg/d , respectively.

Serial MRIs showed some decrease of the contrast-enhancing tumor on coronal images through 11/12/1998. At that time, the enhancing tumor measured 10.98 cm², an 18.1% decrease from baseline. The patient was started on Antineoplaston A10 and AS2-1 capsules (0.5 mg) at that time because repeated subclavian catheter infections prevented further IV ANP therapy. The dosage of ANP therapy was gradually increased to two capsules (1.0 mg) of each formulation qid. Oral therapy was stopped on January 10, 2003. On September 27, 1999 (**Figure 1**), November 18, 1999 (**Figure 2**), and March 27, 2009 (**Figure 2**), the enhancing tumor measured 6.40 cm², 3.80 cm², and 3.00 cm² on coronal images, respectively, which represented a 51.9%,

a 71.4%, and a 77.4% decrease in tumor size. A PR had been achieved by September 27, 1999 and was stable 9.5 years later based on MRI evidence. On August 30, 2021 an email was received from the patient stating that she was doing very well with no evidence of tumor progression. She gave written permission for the use of the figures presented in this article. Without further MRI evidence, we can assume, at a minimum that the PR achieved has lasted 22 years. There is a reasonable possibility that the patient has achieved a CR. The patient experienced one grade 3 serious adverse event (SAE), which was possibly related to ANP therapy, and recovered fully.

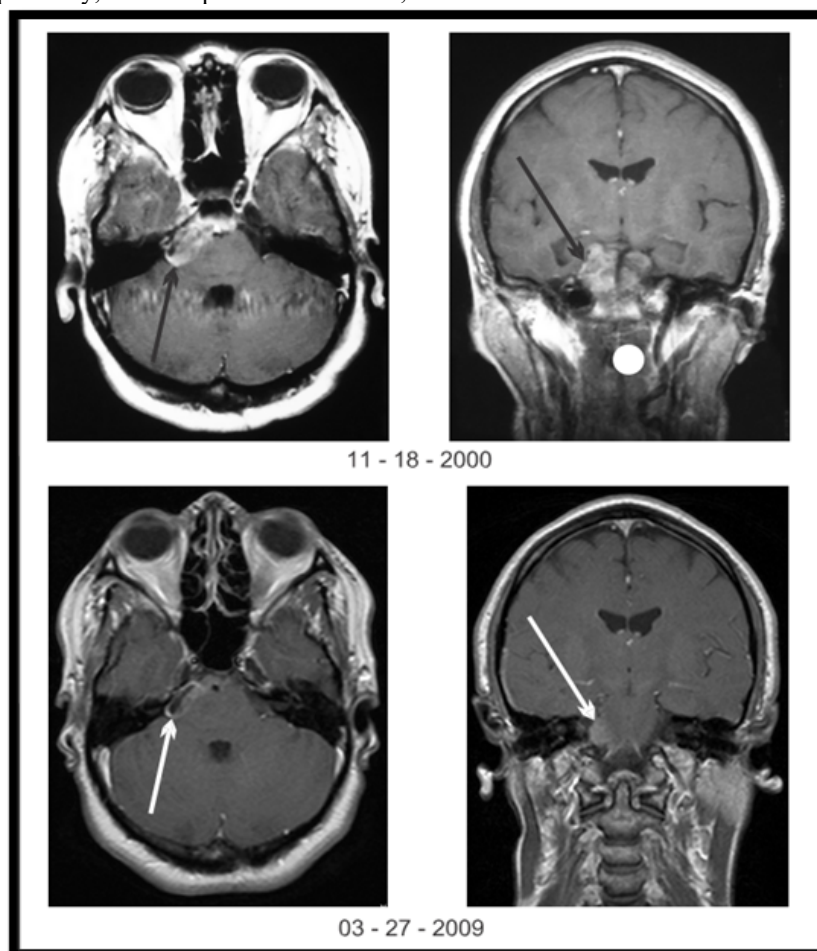


Figure 2. T1 weighted images (axial images on the left; coronal images on the right).

MRI performed at the BC (November 18, 2000) shows a 3.80 cm² enhancing tumor in the same location on coronal imaging as seen in **Figure 1**. This represented a 71.4% decrease in tumor volume when compared to baseline and confirmed the PR to Antineoplaston therapy. The enhancing tumor is also demonstrated in the axial images (see corresponding arrows). MRI performed at the BC (March 27, 2009) shows a 3.00 cm² enhancing tumor in the same location on coronal imaging. This represented a 77.4% reduction in volume when compared to baseline and demonstrated long-term response to ANP therapy. MRI: Magnetic Resonance Imaging; BC: Burzynski Clinic; PR: Partial Response; ANP Therapy: Antineoplaston A10 and AS2-1 (IV and oral).

Antineoplaston 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 Antineoplastons were isolated from the blood and

later from urine [12]. Subsequent studies of the isolated Antineoplastons demonstrated that Antineoplastron A10 (A10, Atengenal) and Antineoplastron AS2-1 (AS2-1, Astugenal) were the most active Antineoplastons. The chemical name of A10 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, Antineoplastron A10 resists the attack of gastric enzymes. In the small intestine, under alkaline conditions, 30% is digested into phenylacetylglutamine (PG) and phenylacetylisoglutamate (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 A10 IV injection. Further metabolism of 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 AS2-1 IV injection [13]. In 1988, following the completion of Phase I studies of A10 and AS2-1, Dr. S. R. Burzynski developed the Phase II protocol designated BT-3 and titled "Therapy of Primary Brain Tumors with Antineoplastron A10 and Antineoplastron AS2-1" The objectives of this protocol were to determine 1) the effectiveness of these Antineoplastons in the control of primary brain tumors and 2) the toxicity of these Antineoplastons in patients with primary brain tumors. On October 4, 1991, three members of the NIH Cancer Therapy Evaluation Program, with an invited neuropathologist and an invited neuroradiologist, visited Dr. Burzynski at the BC to review seven selected brain tumors from Phase I and Phase II studies (including BT-3). Following thorough review, five definite or "possible" CRs were identified [14]. BT-3 led to further Phase II clinical studies, which involved a more aggressive use of ANP therapy, including continuous infusions of higher dose A10 and AS2-1 utilizing ambulatory infusion pumps, as was the case in BT-24.

CONCLUSIONS

In this report, we have presented a 15-year-old female with a recurrent posterior fossa ependymoma, who received ANP therapy, had resolution of her tumor-induced signs and symptoms, achieved a PR by MRI, and has survived for 22 years. ANP therapy has been utilized in a variety of low- and high-grade brain tumors under the Burzynski Research Institute's (BRI's) IND # 43,742. Multiple Phase II protocols have been completed and the impact of ANP on the treatment of brain tumors has been widely published [15-51].

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