Recurrent Pilocytic Astrocytoma: Treatment with Antineoplastons, Complete Response, and > 27 Years Overall Survival

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Received: 05 Feb 2024; Accepted: 02 Mar 2024; Published: 10 Mar 2024

Citation: Burzynski Stanislaw, Burzynski Gregory, Janicki Tomasz, et al. Recurrent Pilocytic Astrocytoma: Treatment with Antineoplastons, Complete Response, and > 27 Years Overall Survival. Recent Adv Clin Trials. 2024; 4(1); 1-7.

ABSTRACT

Rationale: With an incidence of 0.8 per 100,000 people, pilocytic astrocytoma (PCA) is the most common childhood brain tumor. There is no standard therapy for recurrent PCA. The case of a six-year-old child with a recurrent PCA is presented here to detail/discuss the efficacy of ANP therapy (Antineoplaston A10 {Atengenal} and Antineoplaston AS2-1 {Astugenal}) in the treatment of recurrent PCA and to permit a review of the Phase II Protocol BT-13.

Objectives: This patient was treated at the Burzynski Clinic (BC), according to the Phase II Protocol, BT-13, which utilized IV ANP therapy in the treatment of patients with low-grade astrocytomas. 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 the age of 6 years, after gross total resection (GTR) of his PCA performed elsewhere, this male child presented to the BC with recurrent disease and some left-sided weakness. Baseline MRI of the brain performed on January 7, 1979, showed a left cerebellum hemisphere/pons enhancing lesion measuring 2.3 cm x 1.7 cm. On April 25, 1997, after 3 months of IV ANP therapy, the patient’s tumor showed a 53.5% decrease from baseline, indicating a partial response (PR). On December 5, 1997, no enhancing lesion was seen, indicating a complete response (CR). On December 6, 2002, the last follow-up MRI of the brain showed no residual tumor, indicating an enduring CR. The patient has had resolution of his left-sided weakness, has an OS of >27 years since the start of IV ANP therapy, and continues in excellent health.

Conclusions: The utilization of ANP therapy to facilitate a cure in a patient with recurrent PCA is presented. We conclude that ANP therapy is an attractive therapeutic option for children with recurrent PCA.

Keywords
Brain tumor, Low-grade Astrocytoma, Phase II Study, Pilocytic Astrocytoma, Recurrent Pilocytic Astrocytoma, Antineoplastons.

Introduction
Pilocytic astrocytoma (PCA) frequently develops in the posterior fossa, is low-grade, and has a good prognosis [1]. With an incidence of 0.8 per 100,000 people, PCA is the most common childhood brain tumor [2,3]. Up to 60% of PCAs develop in the cerebellum, while nearly 30% develop along the optic pathways or in the hypothalamus, with another 9% developing in the brainstem, and 1-2% developing along the spinal cord [4]. While nearly 20% of neurofibromatosis type 1 (NF1) patients develop PCAs, most PCAs develop from BRAF gene and MAPK signaling pathway alterations [5-9]. PAs are negative for isocitrate dehydrogenase (IDH) and tumor protein p53 (TP53) mutations [1,10].“Pilocytic” derives from the appearance of PCA cells, which have
long, thin bipolar processes that look like hairs [7]. Rosenthal fibers are frequently found on hematoxylin and eosin staining of microscopic sections. Multinucleated giant cells are seen but areas of necrosis are very rarely visualized. PCAs are best imaged by magnetic resonance imaging (MRI) scans of the brain with gadolinium. They are generally well-circumscribed, but 60% or more can infiltrate the surrounding brain tissues, often entering the subarachnoid space through the pia [11,12]. PCAs are periventricular in 82% of cases, 20% show calcification, and 17% are solid with no cystic component [11]. However, in 66% of cases, a significant cystic component with an enhancing nodule is present. The content of a cyst is denser than water because of its proteinaceous nature and the cyst wall will enhance in 46% of PCAs [13,14]. Cerebellar PCAs present with symptoms due to the posterior fossa mass. These symptoms include hydrocephalus with increased cranial pressure, which results in headache, nausea and vomiting, and papilledema. Tumors of the cerebellar hemispheres can also produce intention tremor, ataxia, nystagmus, and dysarthria while tumors of the vermis can produce truncal ataxia and a broad-based gait [15].

Gross total resection (GTR) of a PCA can be curative. Five-year and 10-year survival are > 95% [1]. Serial MRI scans of the brain are used in follow-up. If there is recurrence, a second surgical resection is performed if a significant portion of the recurrent tumor can be removed without disabling neurologic sequelae. Chemotherapy, radiation therapy (RT) and stereotactic radiosurgery (SRS) can also be utilized for recurrent/progressive tumors [16-18].

We present here the successful use of ANP therapy (Antineoplaston A10 {Atengenal} and Antineoplaston AS2-1 {Astugenal}) in the treatment of a recurrent PCA in a six-year-old child following GTR.

Materials and Methods

A 6-year-old male child was in good health until the summer of 1996, when he developed severe and persistent headaches accompanied by vomiting. He underwent an MRI of the brain on August 9, 1996, and underwent GTR of a cerebellar tumor on August 12, 1996. Examination of the microscopic sections of the surgical specimen revealed a PCA. A follow-up MRI of the brain on January 7, 1997, revealed tumor recurrence at the surgical resection site. The child’s parents decided that their son be treated at the Burzynski Clinic (BC). He was evaluated there on January 1, 1997, and began treatment according to protocol BT-13 on January 14, 1997. During his baseline evaluation at the BC, the patient was found to have some left-sided weakness. Lansky Performance Status (LPS) was 90. On January 14, 1997, the patient began intravenous (IV) ANP therapy according to Protocol BT-13, “Phase II Study of Antineoplastons A10 and AS2-1 in Children with Low Grade Astrocytoma.” 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-13 were to 1) determine the efficacy of ANP therapy in children with low-grade astrocytomas 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 of the brain, which were performed every 8 weeks for the first two years, and then less frequently.

Eligibility criteria for BT-13 included 1) Histologic/cytologic diagnosis of incurable low-grade astrocytoma; 2) Tumor size ≥ 5mm; 3) Age > one year and < 18 years; 5) LPS ≥ 60%; and 6) Life expectancy ≥ 2 months.

Gadolinium-enhanced MRI of the brain was used in the diagnosis and follow-up of PCA. T2-weighted, T2-fluid attenuated inversion recovery (T2-FLAIR), T1 weighted, and T1-weighted contrast-enhanced images were obtained. PCAs are generally gadolinium-enhancing, therefore sequential T1-weighted contrast-enhanced images can be utilized to determine the effect of therapy [19,20]. 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 (CDR0000066504, NCT00003468).

Results

Between May 1996 and June 2007, 16 eligible patients were accrued to BT-13 and treated at the BC [22]. The median age was 10.6 years (range: 1.6-17.4 years). Twelve patients were male while four were female. Four patients obtained a CR (25.0%), two patients achieved a PR (12.5%), six patients had SD (37.5%), and 1 (6.3%) patient had PD [22].

The 6-year-old male patient presented here was accrued to BT-13 and began treatment January 14, 1997. Baseline MRI performed January 7, 1997 showed a left cerebellar hemisphere/pons enhancing lesion (Figure 1) measuring 2.3 cm x 1.7 cm (size = 3.91 cm²). His starting dose of A10 was 0.79 g/kg/d. It was gradually increased to 14.34 g/kg/d and subsequently reduced to 13.01 g/kg/d. His starting dose of AS2-1 was 0.21 g/kg/d. It was gradually increased to 0.50 g/kg/d and subsequently reduced to
0.43 g/kg/d. On April 25, 1997, after 3 months of IV ANP therapy, the patient’s tumor measured 1.4 cm x 1.3 cm (size = 1.82 cm²), a 53.5% decrease from baseline, indicating a PR (Figure 1). On April 10, 1998, MRI of the brain showed no enhancing lesion, indicating a CR (Figure 1). IV ANP therapy was discontinued on October 15, 1998. The patient received oral ANP therapy from October 16, 1998, to November 5, 1999. On December 6, 2002, the last follow-up MRI of the brain showed no residual tumor, indicating an enduring CR (Figure 1). The patient now has an OS of > 27 years since the start of IV ANP therapy, has resolution of his left-sided weakness, and continues in excellent health (Figure 2).

Figure 1: Axial MRI Brain Images of Brain: January 7, 1997 - Baseline MRI of the brain showing recurrent left cerebellar hemisphere/pons PCA following GTR – see arrows; April 25, 1997 - Brain MRI performed after three months of ANP therapy showing a 53.5% reduction in the size of the recurrent PCA, indicating a PR – see arrows; April 10, 1998 - MRI of the brain performed after 15 months of ANP therapy showing no enhancing lesions, indicating a CR; December 6, 2002 - the last follow-up MRI of the brain showed no residual tumor, indicating an enduring CR. ANP therapy = Antineoplaston A10 (Atengenal) and Antineoplaston AS2-1 (Astugenal); CR = Complete response; GTR = Gross total resection; MRI = Magnetic resonance imaging; PCA = Pilocytic astrocytoma; PR = Partial response.

Figure 2

Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE v.3). The patient presented here experienced two serious adverse events (SAEs), both of which were not due to ANP therapy, and from which he fully recovered.

Discussion

Chemotherapy, RT, and a second surgical procedure have been utilized in the treatment of recurrent PCA. The use of chemotherapy and RT in recurrent PCA requires further study as the existing data is sparse. However, the use of chemotherapy and RT in newly diagnosed PCA provides some insight. Data from the National Cancer Database (NCDB) for 3865 patients with localized World Health Organization (WHO) grade one PCA from 2004 to 2014 were analyzed. Two hundred and ninety-four received chemotherapy (7.6%), 233 received RT (6.0%), and 42 (1.1%)
received both [23]. On multivariate analysis, chemotherapy was associated with younger age, optic nerve PCAs and a decreased extent of initial surgery. RT was associated with older age, brainstem tumors, and a decreased extent of initial surgery [23].

Utilizing inverse probability of treatment weighting to account for differences in baseline characteristics and Kaplan–Meier analyses with multivariate Cox proportional hazards modeling to analyze overall survival (OS), utilization of chemotherapy and/or RT were associated with a decrease in OS when compared with matched patients treated with surgery alone or observation [23]. Bowers and colleagues, in a retrospective, single institution review, studied the utility of a second surgery for recurrent PCA in 20 cases. Patients who had received adjuvant chemotherapy or RT were excluded from the study. In this group of patients, the median time to tumor recurrence after first surgery was 1.5 years [24].

In the 20 patients studied, the location of the recurrent PCAs was as follows: cerebellum – seven; optic pathway/hypothalamus – five; brainstem – four; cerebral hemisphere – three; and thalamus – one. Regarding second procedures: ten patients underwent a GTR with the location of their tumor being cerebellum – seven, cerebral hemisphere – two, and brainstem one; two patients underwent a near total resection (NTR) with the location of their tumor being cerebellum – one and hypothalamus – one; eight patients underwent a subtotal resection (STR) with the location of their tumor being brainstem – three, hypothalamus – three, optic chiasm – one, and thalamus – one [24]. With a mean follow-up of 40.7 months, eleven patients (55.0%) undergoing second surgery remained tumor free, including both patients undergoing NTR. On the other hand, two patients undergoing GTR (10.0%) and seven patients undergoing STR (35.0%) developed a second recurrence/progression. Following second surgery, five of ten patients (50.0%) with recurrent tumors involving midline structures (brainstem, hypothalamus) and three of ten patients (33.3%) with recurrent tumors involving the cerebellum or cerebral hemisphere developed new neurologic sequelae following second surgery [24].

We present here the successful use of ANP therapy in the treatment of recurrent PCA in a six-year-old child following GTR of the tumor performed elsewhere, thereby avoiding the negative sequelae of chemotherapy, RT, and/or second surgery. 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 [25]. 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-phenylacetylaminoo–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 phenylacetylisoglutamin (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 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 [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 204 mutated genes in the malignant genome and functions as a “molecular switch” which “turns on” tumor-suppressor genes and “turns off” oncogenes [27,28]. Hence, the antineoplastic action of ANP therapy in PCA involves restoration of cell cycle control, induction of programmed cell death, and interference with cancer cell metabolism and nuclear transport.

Conclusions

We have presented the case of a 6-year-old male with a recurrent PCA who obtained a CR with ANP therapy. ANP therapy is an attractive option for patients with recurrent PCA as it avoids the negative sequelae of chemotherapy, RT, and/or second surgery. 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 [29-72]. Based on our findings, we propose further clinical studies of recurrent PCA.

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.

References


Recent Adv Clin Trials, 2024


