Biomedical Research and Clinical Practice

Review Article ISSN: 2397-9631

Persistent pineoblastoma: Complete response and >26 years overall survival in a ten-month-old female treated with antineoplastons

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Abstract

Pineoblastomas account for 24-50% of pediatric pineal parenchymal tumors. They are aggressive, being classified as grade 4 tumors by the World Health Organization (WHO). Objectives: A young female child with persistent pineoblastoma after maximal surgery is presented to 1) demonstrate efficacy of ANP therapy (Antineoplaston A10 {Atengenal} and Antineoplaston AS2-1 {Astugenal}) in treatment of pineoblastoma and 2) review Protocol BT-12, a "Phase II Study of Antineoplastons A10 and AS2-1 in Children with Primitive Neuroectodermal Tumors," which utilized intravenous (IV) ANP therapy. Extensive prior experience with ANP therapy in clinical studies led to its delivery every four hours via subclavian catheter and infusion pump. Tumor response was measured by magnetic resonance imaging (MRI) utilizing gadolinium enhancement and by positron emission tomography (PET). Findings: At ten months of age, this child underwent biopsy of a pineal tumor, which provided the diagnosis of pineoblastoma, ventricular shunting, and sub-total tumor resection, performed elsewhere. Her parents refused a pilot chemotherapy study and, at one year of age, this child presented to the Burzynski Clinic (BC) with persistent disease. Baseline MRI at the BC revealed a measurable enhancing nodule (2.7 cm x 2.2 cm) in the pineal region. IV ANP therapy began in February 1997 and ended in March 2003 when a complete response (CR) was achieved based on PET scan criteria. Subsequently, the child received eight months of oral Antineoplastons as maintenance therapy. At last follow-up, >26 years and two months from diagnosis and >26 years since the start of IV ANP therapy, the patient was healthy, showing no evidence of tumor recurrence. Conclusions: The utilization of ANP therapy to produce a long-lasting CR in a child with persistent pinealoma is presented. We conclude that ANP therapy is an attractive therapeutic option for children with pineoblastoma. Continued study in clinical studies is indicated.

Introduction

Pineoblastomas are primitive neuroectodermal tumors (PNET) located in the pineal region and on histology and imaging closely resemble medulloblastomas and retinoblastomas [1]. Originating from pinealocytes and/or their precursors, they account for 24-50% of pineal parenchymal tumors and typically occur in infants and young children [2,3]. They are the most aggressive pineal parenchymal tumor, being classified as grade 4 tumors by the World Health Organization (WHO) [4]. Magnetic resonance imaging (MRI) frequently shows a >3 cm diameter enhancing tumor with heterogeneous signal intensities and necrotic and hemorrhagic regions [5].

Close to 5% of patients with hereditary retinoblastoma develop midline suprasellar/pineal neuroblastic tumors (trilateral retinoblastoma) [2,6]. Patients with mutation of the DICER1 tumor suppressor gene, have an increased risk for developing pineoblastomas [7].

Approximately 15% of pineoblastomas present with cerebrospinal fluid (CSF) seeding at presentation while also tending to directly involve adjacent brain structures [1]. Due to compression of the cerebral aqueduct, pineoblastomas are almost always associated with obstructive hydrocephalus. Compression of the tectal plate can result in the Parinaud syndrome (upward gaze palsy, absent pupillary response to light, nystagmus) [8]. Other symptoms include headache, ataxia, abnormal behavior, cognitive impairment, and memory loss.

Treatment consists of surgery, radiation therapy (RT) in children >3 years of age, and chemotherapy. In cases of persistent or recurrent disease, stereotactic radiosurgery is frequently utilized [9]. Surgery is performed to relieve hydrocephalus, make a definitive diagnosis, and to remove as much of the tumor as possible without further impairment of the patient's neurologic status. RT is utilized to treat the primary tumor bed as well as the brain and spinal cord because of the possibility of CSF seeding [10]. Stereotactic radiosurgery minimizes the dose delivered to critical adjacent structures and had been proposed as an alternative method of radiation delivery [11]. Chemotherapy (neoadjuvant, chemoradiation, adjuvant) is also utilized in attempt to control tumor growth. The role of chemotherapy remains to be defined. Prospective evaluation is needed [12]. With no standardized therapy for this rare tumor, patients are often treated in clinical trials [9]. We present here the successful use of ANP therapy (Antineoplaston A10 {Atengenal} and Antineoplaston AS2-1 {Astugenal}) in the treatment of a child with a persistent pineoblastoma after maximal surgery.

Materials and methods

At ten months of age, the child presented elsewhere with an inability to gaze upward. She was noted to have increased head circumference

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Key words: *antineoplastons, brain tumor, pediatric pineoblastoma, persistent pineoblastoma, phase II studies*

Received: June 08, 2023; **Accepted:** June 15, 2023; **Published:** June 22, 2023

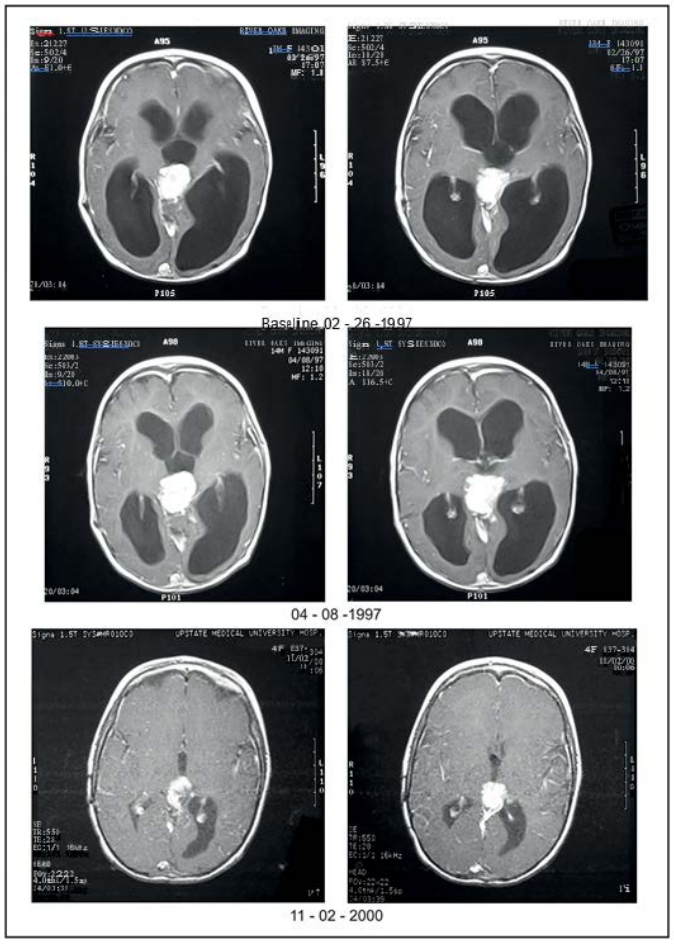

Figure 1. Axial MRI images during before and during ANP therapy [29]**: February 26, 1997 -** Baseline brain MRI showing persistent/progressive pineoblastoma following subtotal resection; **April 8, 1997 –** Six-week follow-up brain MRI showing a 40.1% increase in the size of the persistent/progressive pineoblastoma; **November 2, 2000** – Three-year and 8-month follow-up brain MRI showing a 36.0% decrease in the size of the persistent/recurrent pineoblastoma.
ANP therapy = Antineoplaston A10 (Atengenal) and Antineoplaston AS2-1 (Astugenal); MRI = magnetic resonance imaging.

and bulging of the anterior fontanelle. She was lethargic and irritable, was unable to feed adequately, showed impaired coordination, and had not met her developmental milestones. MRI of the brain on December 18, 1996, showed obstructive triventicular hydrocephalus secondary to a heterogenous, cystic pineal mass, which measured approximately 3.0 cm in maximum diameter and enhanced with gadolinium. Biopsy of the mass was performed, and examination of the microscopic slides confirmed a diagnosis of pineoblastoma. On December 20, 1996, a ventricular shunt was successfully placed, and subtotal resection of the tumor was performed. A computerized tomography (CT) scan of the brain, on December 28, 1996, confirmed that the shunt was in place and there was significant decrease in the child's hydrocephalus (right ventricle > left ventricle). On January 7, 1997, brain MRI showed a measurable and enhancing mass in the pineal region consistent with persistent pineoblastoma. Her parents refused enrollment in a pilot chemotherapy study and at the age of one year, the child presented to the Burzynski Clinic (BC) with persistent disease. She had visual problems, discoordination, and had not met her developmental milestones. On February 26, 1997, baseline MRI at the BC revealed a measurable enhancing nodule (2.7 cm x 2.2 cm) in the pineal region (Figure 1).

The patient began intravenous (IV) ANP therapy according to Protocol BT-12, a "Phase II Study of Antineoplastons A10 and AS2-1 in Children with Primitive Neuroectodermal Tumors." 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-12 were to 1) determine the efficacy of ANP therapy in children with primitive neuroectodermal tumors 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 1) MRI scans, which were performed every 8 weeks for the first two years, and then less frequently, and 2) PET scans as needed.

Eligibility criteria for BT-12 included 1) histologically confirmed primitive neuroectodermal tumor; 2) evidence of persistent/recurrent tumor as determined by gadolinium enhanced brain MRI performed within 2 weeks of study enrollment; 3) Tumor size ≥ 5mm; 4) Age of 6 months to 17 years; 5) Lansky Performance Status (LPS) ≥ 60%; and 6) Life expectancy ≥ 2 months. Gadolinium enhanced MRI of the brain was used in the diagnosis and follow-up of pineoblastoma. T2-weighted, T2-fluid attenuated inversion recovery (T2-FLAIR), T1 weighted, and T1-weighted contrast-enhanced images were obtained. Pineoblastomas are gadolinium-enhancing, therefore 1) sequential T1-weighted contrast-enhanced images and 2) PET scans were utilized to determine the effect of therapy [13].

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 [14]. 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 [14].

Protocol BT-12 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 study is described in Clinicaltrials.gov (CDR0000066492, NCT00003460).

Results

Between April 1966 and January 2005, 13 children were accrued to BT-12 and treated at the BC. Twelve patients were evaluable while one was not evaluable due to technical problems with the follow-up MRIs. Median age was 6.1 years (range: 1.0 to 12.2 years). Ten children were male while 3 were female. Three children obtained a CR, 1 child achieved a PR, 1 child had SD, and 7 patients had PD. Table 1 details the tumor types and responses.

As previously discussed, the child presented here was evaluated at the BC following biopsy of a pineal tumor, which provided the diagnosis of pineoblastoma, and had subsequent placement of a ventricular shunt and a sub-total tumor resection, all performed

Table 1. Tumor Types and Objective Responses in Protocol BT-12 [14].

Type of Tumor	Total Number	Objective Responses		Stable Disease*	Progressive Disease*	Not Evaluable*
		Complete Response*	Partial Response*			
Medulloblastoma	8	1	-	1	6	-
Pineoblastoma	4	1	1	-	1	1
PNET	1	1	-	-	-	-
Totals	**13**	**3**	**1**	**1**	**7**	**1**

*Number

elsewhere. The child was then treated at the BC according to Protocol BT-12, a "Phase II Study of Antineoplastons A10 and AS2-1 in Children with Primitive Neuroectodermal Tumors", which utilized IV ANP therapy in the treatment of these tumors. The starting dose of A10 for this child was 0.91 g/kg/d. The dose was gradually increased to 20.04 g/kg/d and subsequently reduced to 5.05 g/kg/d. Her starting dose of AS2-1 was 0.24 g/kg/d. The dose was gradually increased to 0.65 g/kg/d and subsequently reduced to 0.22 g/kg/d. Upon completion of IV ANP therapy, the child received oral Antineoplastons as maintenance therapy, which was discontinued after eight months.

On April 8, 1997, six-week follow-up brain MRI showed a 40.1% increase in size of the pineoblastoma (Figure 1). On November 2, 2000, three-year and 8-month follow-up brain MRI showed a 36.0% decrease in the pineoblastoma (Figure 1). On February 24, 2003, following six years of IV ANP therapy, PET scan showed no residual hypermetabolic activity in the pineal region indicating a CR (Figure 2). At last follow-up, March 7, 2023, the patient was healthy, had received no other anti-tumor therapy, and showed no evidence of tumor recurrence (Figure 3). Overall survival (OS) has been >26 years.

All MRIs and PET scans of the brain 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), the brain PET scan images (Figure 2), and the post-treatment photograph (Figure 3) presented in this report.

Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE v.3). Ten patients accrued to BT-12 experienced a serious adverse event (SAE). Only two SAEs, a case of edema/fluid retention and a case of somnolence were thought to be due to ANP therapy. The children involved recovered fully. On the other hand, the child presented here experienced no SAEs thought to be due to ANP therapy.

Discussion

Due to the rarity of pineoblastomas, there is little data on associated prognostic factors. Most research studies are small retrospective analyses and case studies, often with children and adults grouped together and/or grouping together of a mixture of pineal region tumor types. Deng et al. [15], used the Surveillance, Epidemiology, and End Results (SEER) database to evaluate prognostic factors for pineoblastomas with the aim of individualizing tumor management

Data from all patients ≤ 17-years-old who were diagnosed with pineoblastoma between 1990 and 2013 was obtained from the SEER registry database. The Cox proportional hazards model was used for both univariate and multivariate analyses, for which survival status was the outcome variable [15]. The study was limited by the lack of detailed data on type and dose of RT and chemotherapy. In addition, all data was gathered retrospectively, resulting in some degree of selection bias. For the years 1990-213, the SEER database included 123 subjects with pediatric pineoblastoma, of which 59 were male (48%) and 64 were female (52%). The median age at diagnosis was 6 years. Seventy-five tumors remained localized (61%), 71 tumors were treated with sub-total resection (58%) and 81 tumors were treated with RT (66%). Deng et al. [15], utilizing multivariate analysis, found age > 5 years (P=0.004) and the use of RT (P=0.000) to be associated with improved survival. When compared to sub-total resection, unknown extent of surgery, or no surgery, i.e., biopsy only, gross total surgical resection (P=0.054) was also associated with improved survival. On the other hand, tumor size > 30 mm in maximum diameter (P=0.025) was associated with a worse outcome. The impact of tumor extension on survival was indeterminate [15].

Other investigators have demonstrated worse outcomes in younger patients [16-18] and the importance of the extent of surgical resection [9,19]. The advantages of RT have been reported in both adults and children [10,17,18]. Pineoblastomas are often treated with craniospinal/whole brain RT, with a total dose of 36 Gray (Gy), followed by a boost to the primary tumor [20]. RT is avoided in children age ≤ 3 years of age because of its adverse effects on the developing brain [11]. For children with pineoblastoma, the role of chemotherapy remains to be defined. Prospective evaluation is needed [12].

In 2020, Liu et al. [21], utilizing methylation analysis, defined four clinically relevant pineoblastoma subgroups. Pineoblastoma subgroups differed in age at diagnosis, propensity for metastasis, cytogenetics, and clinical outcomes. The investigators demonstrated superior outcome in older children with average-risk pineoblastoma who received reduced-dose craniospinal irradiation (CSI) and suggested that the utilization

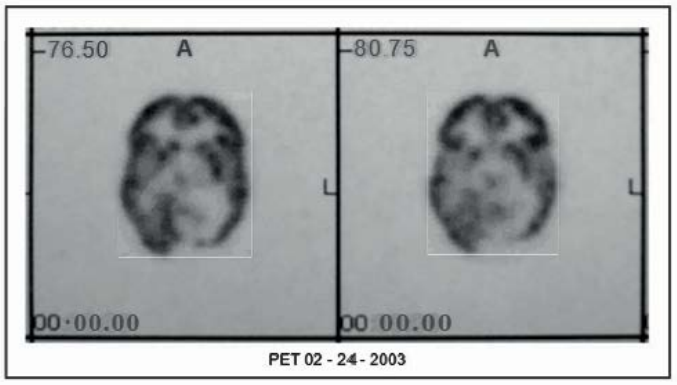

Figure 2. PET scan images after six years of ANP therapy [29]: February 24, 2003 – Pet scan shows no residual hypermetabolic activity in the pineal region indicating a CR. ANP therapy: Antineoplaston A10 (Atengenal) and Antineoplaston AS2-1 (Astugenal); PET: Positron emission tomography; CR: Complete response.

Figure 3. Post-treatment photographs of the patient. **A)** This photograph was taken in 2009 and shows good coordination and good range of motion of her extremities. **B)** This photograph was taken in 2021.

of molecularly defined treatment of pineoblastoma be considered as an option in the future [21].

We have presented the use of ANP therapy in a child diagnosed at age ten months with a very poor prognosis pineoblastoma (age < 5 years, sub-total surgical resection, and not eligible for RT). This child was treated for 6 years with IV ANP therapy and achieved a CR, which, at the time of her last follow-up, had persisted for > 26 years since the start of IV ANP therapy. Antineoplaston (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 [22].

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 [23].

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 [24,25]. Hence, the antineoplastic action of ANP therapy in pineoblastoma involves restoration of cell cycle control, induction of programmed cell death, and interference with cancer cell metabolism and nuclear transport.

Conclusions

We have presented here the case of a ten-month-old female with a persistent pineoblastoma after maximal surgery, who obtained a CR with ANP therapy, suggesting that ANP therapy may be an effective therapeutic option for children with pineoblastoma. 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 [26-66]. Based on the results of Protocol BT-12, cited above, we propose ongoing clinical studies of ANP therapy for children with pineoblastoma.

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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