ABSTRACT

Optic pathway glioma (OPG) is a low-grade tumor developing along the pre-cortical optic pathways and can involve the optic nerve, optic chiasm, optic tracts, and hypothalamus.

Objective: A male child with newly diagnosed and unresectable OPG is presented to 1) review the earliest use of Antineoplastons A10 and AS2-1 for the treatment of brain tumors and 2) demonstrate the efficacy of Antineoplastons in the treatment of OPG. On April 18, 1988, a seven-year-old male child presented to the Burzynski Clinic (BC) with headaches. Based on prior, non-enhanced MRIs and biopsy, an unresectable suprasellar OPG was diagnosed. Antineoplaston therapy was started on a “proof of principle” basis. Tumor response was measured by magnetic resonance imaging (MRI) scans of the brain.

Results: A brain MRI, performed on May 31, 1989, demonstrated an enhancing suprasellar nodule measuring 4.37 cm². On August 24, 1990, brain MRI demonstrated a 0.96 cm² enhancing nodule, indicating the achievement of a partial response (PR). Following higher dose intravenous (IV) and oral Antineoplastons, brain MRI performed on January 24, 1997, demonstrated a residual 0.4 cm² enhancing nodule, indicating an enduring PR. All Antineoplaston therapy was discontinued on August 21, 2000. At last follow-up, > 35 years since the start of Antineoplaston therapy, the patient was healthy and showed no evidence of tumor progression. “Proof of principle” Antineoplaston therapy utilized in a seven-year-old male with unresectable OPG produced an objective response (OR) and prolonged overall survival. Antineoplaston therapy is an attractive therapeutic option for children with OPG.

Keywords: Antineoplastons, Inoperable optic pathway glioma, Low-grade glioma, Phase II studies.

I. INTRODUCTION

Optic pathway gliomas (OPG) are low-grade neoplasms that develop along the pre-cortical optic pathway and may involve the optic nerve, optic chiasm, optic tracts, and the hypothalamus [1]. OPGs account for 3 to 5% of childhood central nervous system (CNS) tumors and most frequently occur in children under ten years of age. They may occur at older ages, but with 90% of cases occurring by 20 years of age. The mean age at presentation is 8.8 years [2], [3]. OPG can occur in 15–20% of NF-1 cases [4]. Chromosomal changes such as deletion of chromosome 17q and neurofibromin (in NF-1 patients), play a role in the development of these tumors [5], [6].

OPGs can be detected on computed tomography (CT) scanning, however, magnetic resonance imaging (MRI) is typically utilized. MRI findings in OPG include an iso- to hypointense tumor on T1-weighted images. hyperintensity is seen on T2-weighted images, and there is usually homogeneous enhancement when gadolinium contrast is administered [7].

Histologically, OPGs are low-grade gliomas with both pilocytic and fibrillary astrocytomas being reported, most being pilocytic [8]. Pilocytic astrocytomas display Rosenthal fibers and eosinophilic granular bodies. Pilomyxoid astrocytomas have also been defined [9]. These tumors show piloid cells in a fibrillary and myxoid background, but Rosenthal fibers are lacking, and eosinophilic granular bodies are rare [9].

Due to the aggressive behavior of OPGs, treatment is considered for most cases. However, in asymptomatic patients, observation and serial imaging is considered the standard of care, as there have been reports of spontaneous regression [10]. In symptomatic patients, complete or subtotal surgical resection of the tumor, chemotherapy, and radiation therapy (RT) for older children are among the treatment modalities utilized for OPG [10].
It is generally agreed that current indications for surgery include single nerve involvement causing progressive proptosis and/or blindness, and chiasm tumors causing mass effect and/or hydrocephalus [11].

Chemotherapy is first-line therapy for children with OPG who experience visual loss, pituitary dysfunction, hypothalamic dysfunction, and progressive disease [12]. A frequently used chemotherapy regimen has been described by Packer and colleagues [13]. Concurrent carboplatin and vincristine are utilized during a 10-week induction phase that is followed by 48 weeks of maintenance carboplatin/vincristine. Packer and colleagues reported that this regime resulted in progression-free survival (PFS) of 75% at 2 years and 50% at 5 years [14].

RT is generally reserved for treatment of progressive OPG in children older than 5–7 years of age [15]. Stereotactic radiosurgery and proton beam RT are as effective as external beam RT and show a significant reduction in side effects [16]. It is generally recommended that children < seven years of age receive chemotherapy as first-line treatment, children between the ages of 7 and 10 years may benefit from initial RT, and children > 10 years of age 10 receive RT as first-line treatment, being treated with 45–50 Gray (Gy) in fractions of 160–200 centi-Gray (cGy) [17].

In a systematic review and meta-analysis of the management of OPG, Yousefi and colleagues reviewed 105 studies, with a total of 4177 patients who underwent different treatments (surgery, chemotherapy, or RT) [18]. The most common complications were due to chemotherapy and RT, including ophthalmologic complications [18]. A “favorable outcome”, i.e., remission in growth, was obtained in 75% of patients.

We present here the successful use of Antineoplastons in the treatment of a male child with an unresectable OPG.

II. METHODS

This young male was in very good health until November 1985 when he developed diplopia, and nausea and vomiting. On November 7, 1985, a CT scan revealed an inoperable suprasellar mass and hydrocephalus. On November 8, 1985, he underwent placement of a ventricular shunt and on November 11, 1985, he had biopsy of the tumor. Examination of the microscopic slides revealed astrocytoma, grade 1.

The child had no conventional treatment for his cancer. Instead, he was treated with a special diet, vitamins, and Laetrile. He did well until March 1988 when he developed headaches. At that time, an MRI scan of the brain, without contrast, revealed a 7.29 cm² tumor in the suprasellar region. His ventricular shunt was replaced, and his headaches improved. His parents elected to take him to the Burzynski Clinic (BC) for evaluation and treatment.

The patient was evaluated at the BC on April 18, 1988, and he was immediately started on Antineoplaston A10 (Astenegal) capsules, intravenous (IV) Antineoplaston AS2-1 (Astugenal), and low dose methotrexate, in a “proof of principle” study. The objectives of this study were to demonstrate the efficacy and safety of Antineoplastons in the treatment of unresectable OPG.

In June 1988, the patient was switched to only IV A10 and AS2-1, which gradually increased to 0.45 g/kg/d and 0.22 g/kg/day, respectively. Antineoplastic capsules alone were instituted on December 10, 1997, and discontinued on August 21, 2000, which ended all Antineoplaston therapy.

Non-enhanced MRIs were used first in the diagnosis and follow-up of this child’s unresectable OPG, but when gadolinium contrast became readily available for use in brain MRIs in children, gadolinium-enhanced MRIs were used to determine his tumor’s response to Antineoplaston therapy. Therefore, T2-weighted, T1 weighted, and T1-weighted contrast-enhanced images were obtained [19]. MRI findings in OPG include an iso- to hypointense tumor on T1-weighted images. Hyperintensity is seen on T2-weighted images, and there is usually homogeneous enhancement when gadolinium contrast is administered [7].

After the introduction of gadolinium contrast enhancement, tumor response to treatment was based on the McDonald criteria [20]. Tumor measurements were obtained from axial post-contrast T1 images. The product of the two greatest perpendicular diameters of each enhancing lesion was calculated and tumor size was defined as the sum of these products [20]. 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 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 enhancing tumor size, or new measurable and enhancing disease, while stable disease (SD) did not meet the criteria for PR or PD [20].

III. RESULTS

The first brain MRI utilizing gadolinium contrast was obtained on May 31, 1989 (baseline MRI) and demonstrated a 6.50 cm² non-enhancing tumor with a 4.37 cm² enhancing nodule seen within the tumor (Fig. 1).

IV Antineoplaston therapy continued and on August 24, 1990, a brain MRI demonstrated a 3.24 cm² non-enhancing tumor with a 0.96 cm² residual enhancing nodule within the tumor, showing a 71.9% decrease from the baseline MRI performed on May 31, 1989, and indicating that a PR had been achieved.

![Fig. 1. Axial MRI images of the brain before, during, and after Antineoplaston therapy.](http://dx.doi.org/10.24018/ejcliniemed.2023.4.5.312)
Following the utilization of increased doses of IV Antineoplaston A10 and AS2-1 and subsequent oral Antineoplastons A10 and AS2-1, a brain MRI was performed on January 24, 1997 (Fig. 1), which demonstrated a 3.30 cm² non-enhancing tumor with a 0.4 cm² residual enhancing nodule within the tumor, showing an 86.2% decrease from the baseline MRI performed on May 31, 1987, and indicating a persistent PR. All Antineoplaston therapy was discontinued on August 21, 2000. The last brain MRI was performed on October 22, 2008 (Fig. 1) and showed only a 0.06 cm² residual enhancing nodule.

All MRI scans of the brain demonstrating an OR were reviewed by a prominent outside neuroradiologist. Consent was obtained from the patient for publication of the brain MRI images (Fig. 1) and the post-treatment photograph (Fig. 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). The child presented here experienced no serious adverse events (SAEs).

IV. DISCUSSION

We have presented the use of Antineoplastons in a young male child with an unresectable suprasellar OPG. This child was treated with Antineoplastons for 8 years and 4 months and achieved a PR after 2 years of therapy. A brain MRI performed 8 years and two months after Antineoplaston therapy was stopped showed only a 0.06 cm² residual enhancing nodule. Overall survival is now > 35 years.

On October 4, 1991, three members of the NIH Cancer Therapy Evaluation Program (CTEP), with an invited neuropathologist and an invited neuroradiologist, visited Dr. Burzynski at the BC to review “proof of principle” Antineoplaston therapy of brain tumors. Following thorough review of seven cases selected by CTEP, five definite or "possible" CRs were identified, as well as one PR, which was achieved by the young male presented here [21].

This “proof of principle” treatment of brain tumors led to a more aggressive use of Antineoplastons, including every-four-hour infusions of IV A10 and IV AS2-1 utilizing subclavian catheters and infusion pumps in Phase II studies.

One such study was BT-23, “Phase II Study of Antineoplastons A10 and AS2-1 Infusions in Children with Visual (Optic) Pathway Glioma,” a one-arm, open-label study [22]. See ClinicalTrials.gov, ID: CDR0000066514. All study subjects had histologically confirmed OPGs, which were not amenable to standard therapy or did not respond to standard therapy. Twelve patients were accrued between June 1996 and May 2004. The median age was 4.5 years (range: 0.6 to 16.6 years). The male:female ratio was 3:1. All study subjects were seen in BC. Four children were not evaluable. Among the evaluable children, two achieved a CR, two achieved a PR, three had SD, and one developed PD. Among evaluable children, the objective response (OR) rate was 33.3% while the disease stabilization rate was 58.3%. Greater than 36 months overall survival was seen in 58.3% of the children while 50% of the children survived more than 60 months.

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 [23]. Subsequent studies of the isolated Antineoplastons demonstrated that Antineoplaston A-10 and Antineoplaston AS2-1 were the most active. 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 phenylacetylglutamin and (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].

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 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 anticancer action of Antineoplaston therapy in OPG involves restoration of cell...
cycle control, induction of programmed cell death, and interference with cancer cell metabolism and nuclear transport.”

V. CONCLUSION

We have presented here the case of a seven-year-old male with an unresectable OPG who obtained a PR with Antineoplaston therapy and is alive and well, without evidence of disease, more than 35 years from the start of therapy, suggesting a CR and cure.

This result plus the results of BT-23 suggest that Antineoplastons may be an effective therapeutic option for children with OPG. 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 [27-68]. Based on the results presented, we propose ongoing clinical studies of Antineoplastons in the treatment of children with OPG.

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CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

REFERENCES


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Antineoplastons were derived from Dr. Burzynski’s early investigations of naturally occurring human peptides, which were deficient in cancer patients. In addition, he has extensive experience treating cancer patients with combinations of targeted agents, immunotherapy, and phenylbutyrate (PB), which targets multiple genetic abnormalities simultaneously.

Dr. Burzynski is the author/co-author of over 300 scientific publications/presentations. He has collaborated with investigators at the NCI, the Medical College of Georgia, the Imperial College of Science and Technology of London, The University of Kurume Medical School in Japan, and the University of Turin Medical School in Italy, among others. He is a member of the American Medical Association, the American Association of Cancer Research (AACR), the American society of Clinical Oncology (ASCO), the Society for Neuroscience, The Society for Neuro-oncology, the Royal Medical Association (U.K.), and the Academy of Medical Ethics.