

Complete Response and Long-Term Survival (>20 Years) of a Child with Tectal Glioma: A Case Report

Stanislaw R. Burzynski Gregory S. Burzynski Tomasz J. Janicki Ania Marszalek

Burzynski Clinic, Houston, Tex., USA

Established Facts

- Tectal glioma is the smallest deadly tumor in the body.
- There is no curative treatment.

Novel Insights

- This is the first report of effective treatment for tectal glioma.
- The treatment with antineoplastons accomplished over 12 years of tumor-free survival.

Key Words

Antineoplastons A10 and AS2-1 · Brain tumor · Brainstem glioma · Phase II trial · Tectal glioma

Abstract

Tectal glioma is a midbrain tumor. The patient generally presents with symptoms related to increased intracranial pressure and requires treatment for hydrocephalus. No effective pharmacological treatments have yet been introduced. This report discusses a case of a 13-year-old male diagnosed with tectal glioma who obtained a complete response and long-term survival after the treatment with antineoplastons (ANP) in phase II trial. Prior treatment consisted of placement of a ventriculoperitoneal shunt. After

6 years of stabilization there had been an increase in tumor size with signs of malignant transformation. The patient received treatment with ANP A10 and AS2-1 infusions for 20 months, obtained a complete response, and was switched to maintenance with ANP capsules. All treatments were discontinued in December 2003. Adverse events according to CTCAE v3.0 included: hypernatremia (two events of grade 3, one event of grade 2, four events of grade 1), one case of fatigue (grade 2), and one allergic reaction (grade 1). Currently, over 20 years from his diagnosis and over 13 years from treatment start he is symptom-free and leads a normal life. This report indicates that it is possible to obtain long-term survival of a child with tectal glioma with currently available investigational treatment.

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Introduction

Tectal glioma is a subtype of midbrain brainstem glioma which typically represents an exophytic mass extending from the quadrigeminal plate [1]. Histologically it includes pilocytic, fibrillary, low-grade or anaplastic astrocytoma [2]. The patients generally present with symptoms related to increased intracranial pressure and require effective treatment for hydrocephalus [3]. No effective pharmacological treatments have yet been recommended. Here we discuss a case of tectal glioma with long-term overall survival and a complete response (CR) after treatment with antineoplastons (ANP), which are synthetic analogs of naturally occurring amino acid derivatives that have inhibitory effects on neoplastic growth [4, 5].

Case Report

A 20-year-old Caucasian male (date of birth February 19, 1981) presented to Burzynski Clinic in August 2001, with a long history of brain tumor. In January 1994, the patient was evaluated for a mild learning disability. Two months later he developed coarse tremors in the upper extremities. After 6 months, he was evaluated at a local family care center and was found to have symmetrical tremors in the upper extremities, and difficulty with rapid alternating movements. Shortly thereafter, he was admitted to the local university hospital for massive hydrocephalus with aqueduct obstruction by an unresectable tectal tumor. On the same day, he underwent placement of a ventriculoperitoneal shunt, which relieved his hydrocephalus. The evaluation at the local university hospital provided the final diagnosis of tectal glioma, most likely low-grade astrocytoma. Biopsy and surgery were not recommended, but the patient was advised to have periodical follow-ups. Three months later, he underwent neurosurgical consultation with no recommendation for surgical intervention except for occasional shunt revision. In April 1995 he was consulted by a neuro-oncologist at a leading neuro-oncology treatment center in the US. Since the tumor did not change in size, there was no further recommendation for treatment, but only for periodical follow-up.

Magnetic resonance imaging (MRI) of the head of September 30, 1997, revealed approximately the same size tectal tumor measuring $17 \times 17 \times 15$ mm. MRI of June 21, 2001, indicated transformation to a vascular tumor and increasing tumor size. The patient underwent neurosurgical consultation at a state university hospital, and his case was discussed by the tumor board, which concluded that the tumor had acquired high-grade glioma characteristics, and that the patient should receive radiation therapy and chemotherapy with temozolomide. Surgical resection was not recommended. Shortly thereafter, in July 2001, he underwent consultation at a university hospital with the recommendation of radiation therapy without chemotherapy.

On August 7, 2001, the patient was admitted for evaluation at Burzynski Clinic in Houston, Tex. He was complaining of occasional headaches below the occipital area, occasional blurred vi-

sion, and slight ptosis of the left eyelid. There was no significant past medical history, and no neurofibromatosis, type 1. His physical examination was grossly within normal range. His Karnofsky Performance Status was 80. Baseline MRI of July 27, 2001, revealed over 60% increase in the size of the contrast-enhancing lesion compared to the prebaseline study of June 21, 2001.

On August 14, 2001, the patient was admitted for treatment with ANP A10 and AS2-1 infusions according to Protocol BT-09. After initial progression, partial response was observed on August 14, 2002, followed by CR on December 4, 2002. Five months later the patient was eligible for maintenance oral treatment with ANP A10 and AS2-1 capsules.

The study was listed by the National Cancer Institute and reviewed by an independent institutional review board (BRI Institutional Review Board), and all of the study subjects read, understood, and signed a written informed consent prior to enrollment. This study was conducted in accordance with the US 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, and the FDA's Guidance for the Industry. The study was sponsored by the Burzynski Research Institute and conducted by the Burzynski Clinic in Houston, Tex. The patient did not pay for the investigational agents. Treatment data are summarized in table 1.

Before coming for the treatment with ANP, the patient was taking oral dexamethasone 16 mg daily. He continued such treatment together with intravenous ANP, and 2 weeks later, he increased the dose to 24 mg orally daily to reduce intracranial pressure. After 2 months, the dose of dexamethasone was decreased again to 12 mg daily, and the patient began gradual tapering of the doses of dexamethasone until he discontinued 2 months later.

From August 14, 2001 to September 2, 2001, the patient was also taking oral famotidine 40 mg daily. Three and a half months after the treatment start, he developed an infection of his subclavian catheter, for which he was treated with intravenous antibiotics (vancomycin, gentamicin and rifampin). The infection resolved within a week. He was also periodically taking potassium, magnesium, calcium and phosphate supplements due to electrolyte abnormalities.

Adverse events according to CTCAE v3.0 included: hypernatremia (two events of grade 3, one event of grade 2, four events of grade 1), one case of fatigue (grade 2), and one allergic reaction (grade 1). All adverse events were reversible.

Baseline MRI of the head revealed a contrast-enhancing mass measuring 2.2×2.2 cm, located in the tectum. After 2 months of treatment there was an increase in the size of the lesion by 45% as evidenced by MRI of October 12, 2001. The tumor growth stabilized after the dose of ANP A10 was increased, as indicated by three follow-up MRIs at 1-month intervals. An MRI of the head after 7 months of treatment revealed an approximate 20% decrease in the tumor size, and since then there was gradual shrinkage of the lesion evidenced by MRIs taken at 1- to 2-month intervals. At 1 year, there was over 60% decrease in tumor size, which qualified the patient for partial response. Finally, on December 4, 2002, there was no visible tumor on the MRI. He was followed by MRIs every 2–3 months, as required by protocol, with no sign of tumor recurrence (fig. 1). Five years after treatment discontinuation, the MRI on November 19, 2008, revealed a small cystic for-

Table 1. Treatment data

Date	Comment	ANP A10 and AS2-1 i.v., g/kg/day		ANP A10 and AS2-1 oral, g/kg/day		Dexamethasone oral, mg/day
		A10	AS2-1	A10	AS2-1	
August 14, 2001 till August 29, 2001	escalation and target dose	8.2	0.4	–	–	16
August 30, 2001		8.2	0.4	–	–	24
October 18, 2001 to December 1, 2001	increase of the dosage of A10	12.5	0.4	–	–	reduced from 24 to 12 on October 26, 2001 followed by a gradual decrease in the dosage from November 1, 2001 and permanent discontinuation on December 26, 2001
December 22, 2001 to April 20, 2003		8.0–14.7 median 11.6	0.3–0.4 median 0.34	–	–	–
April 20, 2003		discontinued		–	–	–
April 22, 2003 to December 26, 2003		–	–	0.26	0.26	–
December 27, 2003		–	–	discontinued		–

Patient's date of birth: February 19, 1981. Off treatment December 2, 2001 to December 21, 2001 due to catheter infection, and from August 27, 2002 to September 6, 2002 and from March 14, 2003 to March 24, 2003 due to suspected gastrointestinal infection.

mation measuring 0.5×0.4 cm. It persisted without any treatment until December 2010, when the MRI did not show any lesions, confirmed by the most recent MRI in December 2012. The MRIs were performed and evaluated by external radiologists. After completion of the treatment, all scans were submitted for central radiology review at Innovative Radiology in Houston, Tex., USA. It was the opinion of the central radiology review that the patient obtained a CR, and the residual changes represented post-therapy gliosis and calcifications. The response was judged by the decrease and disappearance of the contrast-enhancing and non-enhancing tumor and by the negative positron emission tomography (PET) scan. CR required confirmation by a second MRI performed at least 4 weeks later. Post-therapy gliosis and calcifications present on the MRI of December 8, 2012, were not considered to represent active tectal glioma. The patient's response data are summarized in table 2. The patient became asymptomatic after 7 months of treatment after his MRI of the head revealed the decreased tumor size. He continues to live a normal life and work full-time at present. He has a good family life and became the father of two children.

Discussion

Tectal gliomas occupy the tectum or quadrigeminal plate, which is composed of the superior and inferior colliculi. Since they lie posterior to the cerebral aqueduct,

they frequently cause obstruction of the circulation of cerebrospinal fluid and hydrocephalus [3]. There is usually a benign course of the disease but, unfortunately, tectal glioma is known as the smallest tumor in the body that can lead to death of the patient [1]. The initial clinical history of the patient described in this article is typical for benign tectal glioma. It is characterized by stable tumor size over a long period of time and uncommon cranial nerve symptoms. The management of these tumors is typically limited to placement of a ventriculoperitoneal shunt. In this case the patient had relatively minor symptoms during the first 8 months, but required a ventriculoperitoneal shunt after he developed massive hydrocephalus. There was no significant change in the tumor size for over 6 years, but after that there was over 60% increase in tumor size and signs of malignant transformation by MRI. Surgery and biopsy were not advised in this case since some reports indicated rapid tumor growth after surgical intervention [6, 7]. Based on prior experience in the treatment of both benign and aggressive pediatric gliomas, the patient was admitted to clinical study according to Protocol BT-09 [4, 5, 8]. He accomplished durable CR with long-term survival (over 20 years from tumor diagnosis). He lives a normal, productive life and did

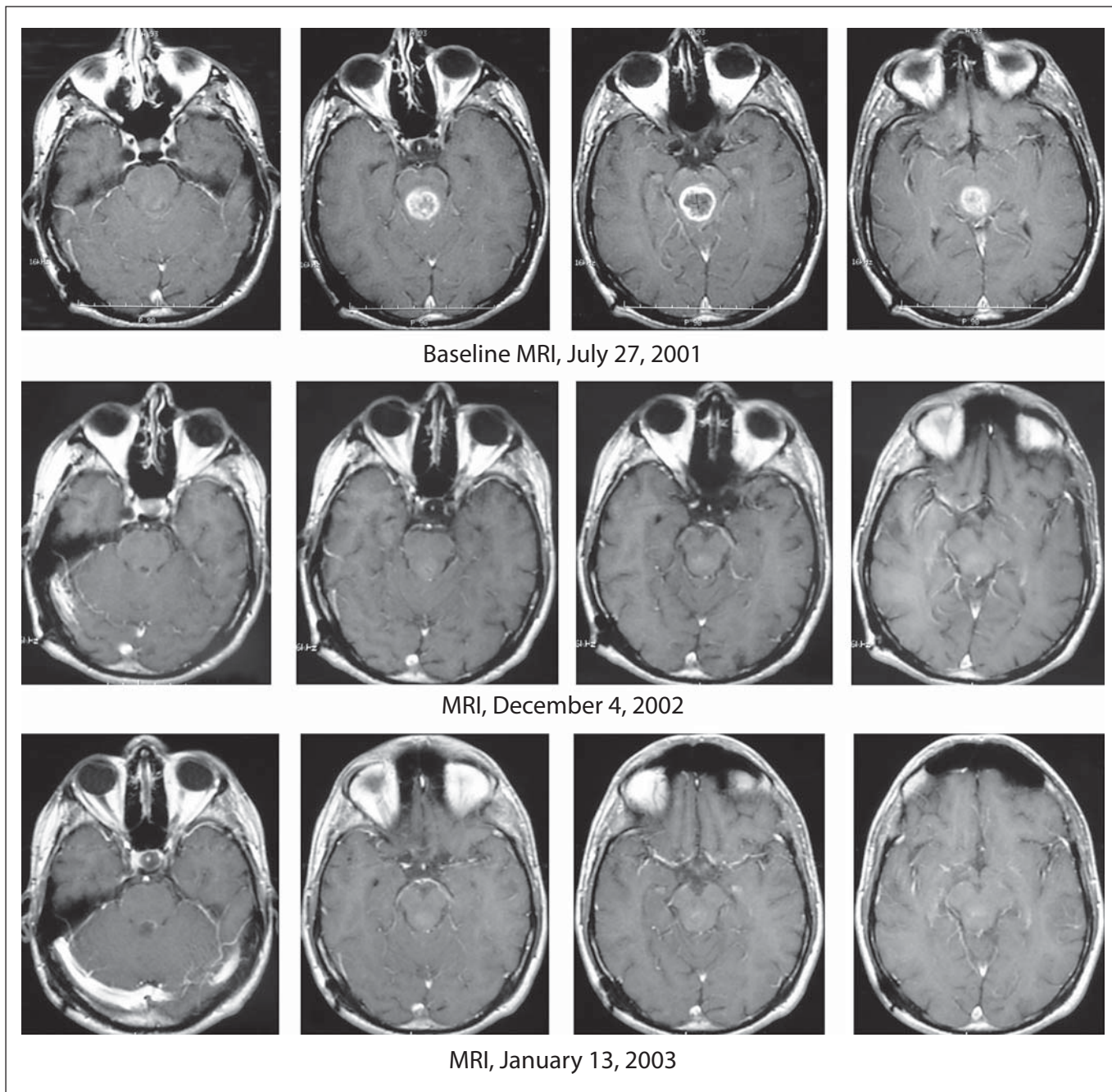


Fig. 1. Baseline MRI and follow-up postcontrast MRIs indicating response to treatment.

not show any chronic toxicity. The patient was not diagnosed with neurofibromatosis, type 1, which could promote spontaneous regression. His last follow-up was on September 15, 2014. Biopsy and surgery were not recommended by neurosurgical consultants, and it is disappointing that pathology data are not available. The au-

thors decided to delay writing this report, to make sure that the results would be most convincing. This report suggests that it is possible to obtain long-term overall survival in patients suffering from tectal glioma with an aggressive course of the disease. The results of phase II studies of ANP are described in a number of articles [8–10].

Table 2. Response data

Date	MRI enhancing	MRI nonenhancing	PET	Response	Confirmation by CRR
July 27, 2001	2.1 × 2.2 cm			baseline	
October 12, 2001	increased by 45% 2.6 × 2.7 cm	increased		increasing tumor size	increased
November 9, 2001	stable 2.6 × 2.4 cm	stable			increased
December 13, 2001	stable 2.6 × 2.4 cm	stable			stable
January 17, 2002	stable 2.6 × 2.4 cm	stable			stable
February 27, 2002	decreased by 20% 2.5 × 2.2 cm	decreased		SD	decreased
August 14, 2002	decreased by 64% 1.5 × 1.1 cm	decreased		PR	PR
December 4, 2002 till December 8, 2012	no visible tumor, on 11/19/2008 visible small cystic formation, 0.5 × 0.4 cm, resolved on 12/31/2010	no visible tumor	CR confirmed by PET on 1/3/2003 and 12/8/2012	CR	CR

Patient's date of birth: February 19, 1981. CR = Complete response; CRR = central radiology review; PR = partial response; SD = stable disease.

Disclosure Statement

The clinical trial was sponsored by the Burzynski Research Institute (BRI) Inc. S.R.B. is chairman of the Board of Directors and President of BRI Inc. G.S.B. is a member of the Board of Directors

of BRI Inc. T.J. is the Vice President of Clinical Trials at BRI Inc. All authors are employed by Burzynski Clinic. Randall A. Stenoien, MD, who is employed by Innovative Radiology of Houston, Tex., provided the central radiology review. Innovative Radiology is not associated with Burzynski Clinic or BRI.

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