

# Targeted Therapy With Antineoplastons A10 and AS2-1 of High-Grade, Recurrent, and Progressive Brainstem Glioma

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**Background:** Brainstem glioma carries the worst prognosis of all malignancies of the brain. Most patients with brainstem glioma fail standard radiation therapy and chemotherapy and do not survive longer than 2 years. Treatment is even more challenging when an inoperable tumor is of high-grade pathology (HBSG). The objective of this report is to summarize the outcome of patients with HBSG treated with antineoplastons in 4 phase 2 trials. **Patients:** The following group of 18 patients was evaluable: 4 patients with glioblastomas and 14 patients with anaplastic HBSG. Fourteen patients had diffuse intrinsic tumors. Twelve patients suffered from recurrence, and 6 patients did not have radiation therapy or chemotherapy. **Methods:** Antineoplastons, which consist of antineoplaston A10 (A10I) and AS2-1 injections, were given in escalating doses by intravenous injections. The median duration of antineoplaston administration was 5 months, and the average dosage of A10I was 9.22 g/kg/d and of AS2-1 was 0.31 g/kg/d. Responses were assessed by gadolinium-enhanced magnetic resonance imaging and positron emission tomography. **Results:** The overall survival at 2 and 5 years was 39% and 22%, respectively, and maximum survival was more than 17 years for a patient with anaplastic astrocytoma and more than 5 years for a patient with glioblastoma. Progression-free survival at 6 months was 39%. Complete response was achieved in 11%, partial response in 11%, stable disease in 39%, and progressive disease in 39% of patients. Antineoplastons were tolerated very well with 1 case of grade 4 toxicity (reversible anemia). **Conclusion:** Antineoplastons contributed to more than a 5-year survival in recurrent diffuse intrinsic glioblastomas and anaplastic astrocytomas of the brainstem in a small group of patients.

**Keywords:** brainstem glioma; glioblastoma; GBM; astrocytoma; glioma; brain tumor; antineoplastons; ANP

Brainstem gliomas (BSGs) occur primarily in children, represent from 10% to 20% of all primary tumors of the central nervous system, and carry the worst prognosis of all malignancies of the brain.<sup>1,2</sup>

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They remain inoperable and incurable, and the only palliative treatment of newly diagnosed tumors is standard radiation therapy.<sup>3,4</sup> Effective treatments do not exist for recurrent BSG.<sup>5,6</sup> High-grade glioma pathology (HBSG) contributes to the rapid progression of the disease and results in a poor prognosis because of both the location and the aggressiveness of the tumor.<sup>4</sup> Most patients with newly diagnosed HBSG do not survive more than 2 years, and patients with recurrent tumors survive no more than 6 months despite standard treatment.<sup>4,6</sup> New strategies employing a multitargeted approach may offer better results for these tragic tumors.<sup>7-11</sup> Among these new multitargeted agents is the treatment with antineoplastons A10 (A10I) and AS2-1 (ANP), which are synthetic analogs of naturally occurring sodium salts of phenylacetylglutamine (PG), phenylacetylisoglutamine, and phenylacetic acid (PN).<sup>12</sup> ANP affects the RAS, AKT, TP53, PTEN, INI1, p21, MYCC, and apoptosis pathways. The proposed mechanism of action of ANP involves a decrease of DNA instability and amplification of oncogenes through normalization of global methylation of the genes by A10I (PG) and activation of silenced tumor suppressors through inhibition of methylation of their promoters and deacetylation of histones by AS2-1 (PN).<sup>7,12,13</sup> In addition, both PG and PN promote apoptosis of neoplastic cells (Figure 1). Additional mechanisms that are involved include inhibition of farnesylation of the p21 protein of the RAS oncogene by PN, normalization of nuclear transport of the mutated INI1 protein, and deamidation of BCL-X<sub>L</sub> by PG.<sup>7,13</sup>

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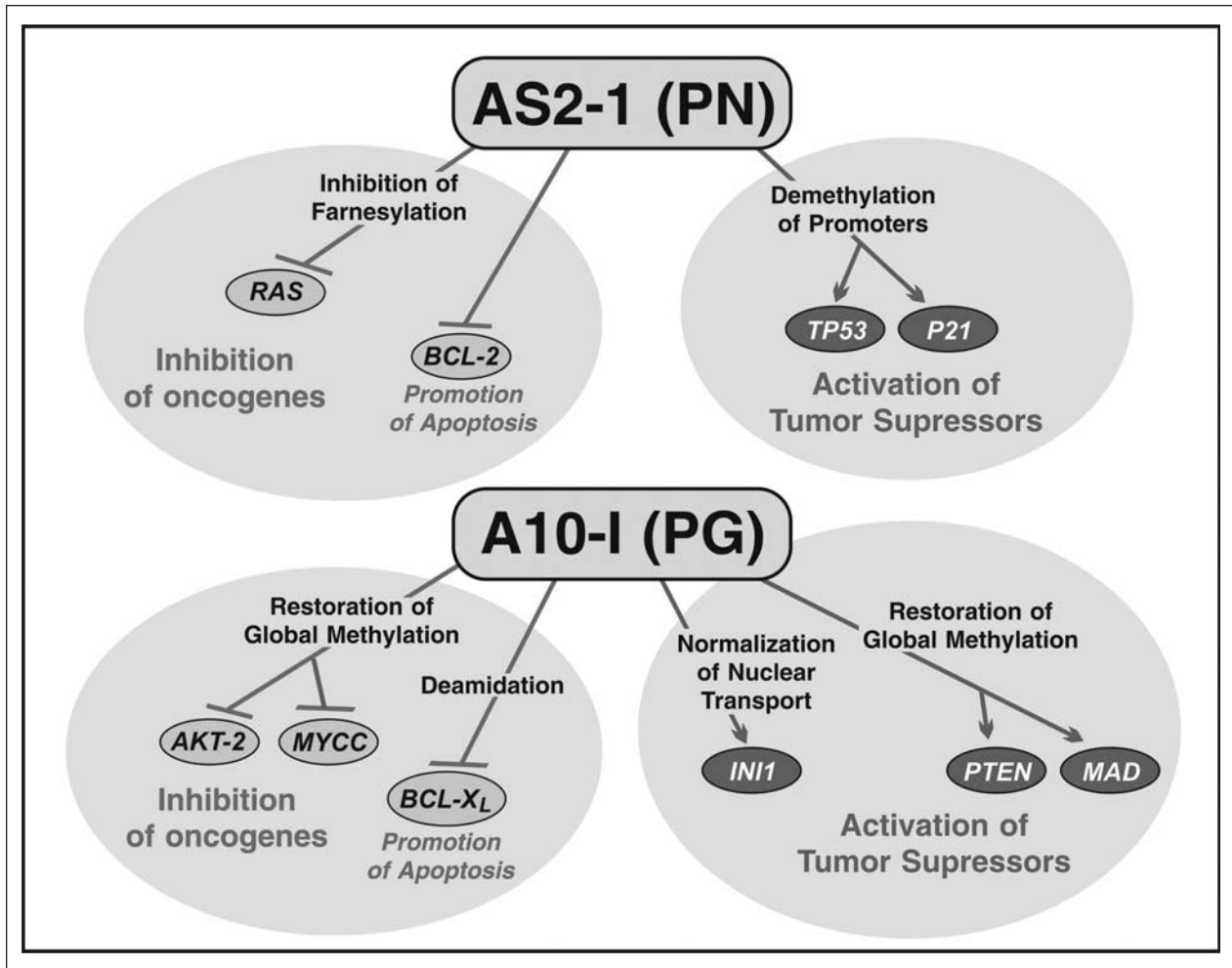


Figure 1 The proposed mechanism of antitumor activity of antineoplastons (ANPs) in high-grade glioma pathology (HBSG). Phenylacetic acid (PN; the active ingredient of antineoplaston AS2-1) inhibits farnesylation of protein p21 of the RAS oncogene, inhibits RAS and BCL-2, and activates the tumor suppressor genes TP53 and p21 through demethylation of their promoters. Phenylacetylglutamine (PG; the main ingredient of antineoplaston A10 I) restores global methylation of DNA, inhibits the oncogenes AKT2 and MYCC, activates the tumor suppressor genes PTEN and MAD, and restores activity of the mutated INI1 protein through normalization of nuclear transport. Both PN and PG promote apoptosis: PN through inhibition of BCL-2 and PG through deamidation of the BCL-X<sub>L</sub> protein.

The objective of this report is to summarize the outcome of patients with HBSG treated with ANP in 4 phase 2 trials.

## Patients and Methods

### Patients

A total of 18 evaluable patients diagnosed with HBSG were treated with ANP in phase 2 clinical trials monitored by the Food and Drug Administration (FDA) and the Institutional Review Board (IRB) of the Burzynski Research Institute. Table 1 shows a summary of patient characteristics, and Table 2 shows individual patient characteristics. Four patients were diagnosed with glioblastoma multiforme (GBM), and 14 patients were diagnosed with anaplastic HBSG; 14

patients had diffuse, intrinsic tumors, and 12 patients suffered from tumor recurrence. Six patients did not have radiation therapy or chemotherapy (1 underwent a biopsy only, and 5 underwent surgical resection). Diagnoses were confirmed by pathologists not affiliated with the Burzynski Clinic (BC).

### Patient Assessment

Pretreatment patient evaluation performed within 7 days of study enrollment included a complete medical history and physical examination; complete blood count and differential; prothrombin and partial thromboplastin times; a biochemical profile that included blood urea nitrogen, creatinine, uric acid, electrolyte, and glucose levels; standard liver function tests; determination of the levels of antiepileptics; uri-

**Table 1. Summary of Patient Characteristics (N = 18)**

Characteristic (N = 18)	n	%
Gender		
Male	8	44
Female	10	56
Age, y		
Range	2-42	
Median	10	
Tumor history		
Anaplastic astrocytoma	13	72
Anaplastic astrocytoma/mixed glioma	1	6
GBM/BSG	4	22
Tumor size at baseline, cm <sup>2</sup>		
Median	9.25	
Previous therapies		
SU/CH/RA	4	22
SU/RA	4	22
CH/RA	1	6
SU	5	28
Bx/CH/RA	2	11
Bx/RA	1	6
Bx	1	6
Karnofsky Performance Status		
Range	40-90	
Median	50	

Patients were admitted between July 12, 1988, and November 13, 2003. Data are as of June 10, 2005. GBM = glioblastoma multiforme; BSG = brainstem glioma; SU = surgery; CH = chemotherapy; RA = radiation therapy; Bx = biopsy.

analysis; and baseline magnetic resonance imaging (MRI) of the head.<sup>7,14,15</sup>

## Treatment

### Protocol Design

Patients with high-grade, recurrent, and progressive BSGs were treated and analyzed from the following 4 different studies: BT-03, BT-11, BT-18, and CAN-01. The design and results of the BT-03 and CAN-01 studies, which are already completed, have been published previously.<sup>14,15</sup> Only single patients were treated under BT-03, BT-18, and CAN-01. Protocols BT-11 and BT-18 (still ongoing) shared the same design including evaluation criteria, except BT-11 was opened for patients with BSGs and BT-18 for patients with mixed gliomas (1 of the patients enrolled in BT-18 was diagnosed with a mixed glioma of the brainstem). The remaining patients were accrued to protocol BT-11.<sup>7</sup>

### Treatment Plan

Treatment involved daily intravenous injections of A10I and AS2-1, and during the first 3 weeks, ANP was administered at the BC. All patients (or guardians) signed informed consent forms, which were reviewed by the FDA and approved by the IRB. The injections were administered every 4 hours through a subclavian venous catheter via a dual-channel infusion pump. The average maximum dosage of A10I was 13.37 g/

kg/d (SD = 7.36 g/kg/d) and 0.49 g/kg/d (SD = 0.26 g/kg/d) of AS2-1. The patients' caretakers underwent training in the programming of the pump and standard central venous catheter care. After the first 3 weeks, the treatment continued under the care of local subinvestigators. Daily monitoring was performed for compliance and toxicity, which was graded based on the National Cancer Institute Common Toxicity Criteria. The details of ANP administration and monitoring have been described previously.<sup>7,12,15</sup>

### Evaluation of Treatment Efficacy

Evaluation of patient responses was based on MRIs of the head for all protocols and in some cases was confirmed by positron emission tomography (PET) scans. The response criteria are defined as follows:

**Progression-free survival:** The time interval measured from the date of initiation of ANP to the date of progressive disease, death, or the last contact with the patient.

**Overall survival:** Measured from the initial date of diagnosis.

**Complete response:** Complete disappearance of all contrast-enhanced tumor(s) on imaging studies for at least 4 weeks duration while receiving no corticosteroids.

**Partial response:** More than a 50% decrease in the sum of the products of the greatest perpendicular diameters of the contrast-enhanced tumor(s) for at least 4 weeks duration with no appearance of new lesions while on a decreasing or stable dose of corticosteroids.

**Stable disease:** Less than a 50% change (either greater or smaller) in the sum of the products of the greatest perpendicular diameters of the contrast-enhanced tumor(s) compared with nadir evaluation or the appearance of new lesions.

**Progressive disease:** More than a 50% increase in the sum of the products of the greatest perpendicular diameters of the contrast-enhanced tumor(s) or appearance of a new lesion(s).

**Objective response:** complete response, partial response, and stable disease.

In all cases of complete response and partial response, the responses were confirmed by radiologists not affiliated with the BC.

### Statistics

The studies under FDA- and IRB-reviewed protocols were considered as the source of all cases described in this article. Response rates, survival statistics, incidences of adverse events, maximum dosages, average dosages, duration of treatment, and summary of the patients' statistics were obtained using Microsoft Excel 97 and Access 02, MedCalc Version 8.0.0.0 (MedCalc Software, Mariakerke, Belgium).

**Table 2. Individual Patients' Characteristics**

Case	Protocol	Sex	Age, <sup>a</sup> y	Date of Initial Diagnosis	Tumor Type	Tumor Type Dissemination	Recurrence	KPS Baseline	Previous Treatment		
									SU	CH	RA
1	BT-03	F	36	Jul 29, 1987	Anaplastic astrocytoma	DBSG	Recurrent	60	Yes	Yes	Yes
2	BT-11	F	7	Jul 17, 1998	Anaplastic astrocytoma	DBSG	—	80	Yes	No	No
3	BT-11	M	5	Oct 2, 2003	Anaplastic astrocytoma	DBSG	—	60	Yes	No	No
4	BT-22	F	13	Dec 24, 1997	Anaplastic astrocytoma	Multifocal	Recurrent	40	Yes	Yes	Yes
5	BT-18	F	29	Sep 15, 1992	Anaplastic/mixed glioma	DBSG	Recurrent	80	Yes	Yes	Yes
6	CAN-01	F	5	Jan 9, 1996	Anaplastic astrocytoma	DBSG	—	80	Yes	No	No
7	BT-11	F	5	Feb 18, 1997	Anaplastic astrocytoma	Exophytic	Recurrent	90	Yes	No	Yes
8	BT-11	M	25	Oct 20, 1997	Anaplastic astrocytoma	DBSG	Recurrent	50	Bx	No	Yes
9	BT-11	F	25	Apr 24, 1998	Glioblastoma multiforme	Cervico-medullary	Recurrent	50	Yes	No	Yes
10	BT-11	M	42	Jan 6, 1989	Anaplastic astrocytoma	DBSG	Recurrent	40	Bx	Yes	Yes
11	BT-11	M	12	Apr 7, 1999	Glioblastoma multiforme	DBSG	—	50	Yes	No	No
12	BT-11	M	40	Jun 3, 1999	Glioblastoma multiforme	DBSG	Recurrent	50	Yes	No	Yes
13	BT-11	F	15	Dec 29, 1997	Glioblastoma multiforme	DBSG/multifocal	Recurrent	50	Yes	No	Yes
14	BT-11	M	2	Feb 20, 2001	Anaplastic astrocytoma	DBSG	—	60	Yes	No	No
15	BT-11	M	3	Jan 11, 2001	Anaplastic astrocytoma	DBSG	—	50	Bx	No	No
16	BT-11	M	4	Apr 1, 2002	Anaplastic astrocytoma	DBSG	Recurrent	50	Bx	Yes	Yes
17	BT-22	F	7	Dec 13, 1999	Anaplastic astrocytoma	Exophytic	Recurrent	50	Yes	Yes	Yes
18	BT-11	F	8	May 1, 2001	Anaplastic astrocytoma	DBSG	Recurrent	40	No	Yes	Yes

Patients were admitted between July 12, 1988, and November 12, 2003. Data are as of June 10, 2005. KPS = Karnofsky Performance Status; SU = surgery; CH = chemotherapy; RA = radiation therapy; DBSG = diffuse, intrinsic brainstem glioma; Bx = biopsy.

a. Age at admission.

**Table 3. Summary of Treatment Data With Antineoplastons**

Case	Start Date	Stop Date	Days On <sup>a</sup>	Average Dosage, g/kg/d	
				A101	AS2-1
1	Jul 12, 1988	Jan 21, 1990	551	0.78	0.37
2	Aug 13, 1998	Nov 2, 1998	71	7.79	0.34
3	Nov 12, 2003	May 7, 2004	152	17.78	0.4
4	Oct 1, 1999	Nov 3, 2001	245	6.54	0.31
5	Jul 17, 1996	Dec 28, 1996	156	5.96	0.24
6	Jan 31, 1996	Aug 14, 1996	163	13.02	0.27
7	Apr 17, 1997	Jul 30, 1997	94	10	0.36
8	Apr 15, 1998	Apr 23, 1999	331	5.97	0.24
9	Mar 11, 1999	Sep 21, 1999	148	10.16	0.3
10	Mar 19, 1999	Sep 14, 1999	162	4.18	0.2
11	Apr 20, 1999	Mar 20, 2000	145	4	0.3
12	Sep 30, 1999	Aug 21, 2001	650	5.28	0.25
13	Dec 29, 1999	Jun 1, 2000	94	6.59	0.21
14	Mar 23, 2001	Jun 29, 2002	440	18.3	0.33
15	Mar 28, 2001	May 23, 2001	56	9.78	0.28
16	Aug 7, 2002	Dec 26, 2002	128	19.44	0.52
17	Jun 22, 2000	Aug 11, 2000	46	13.1	0.43
18	Sep 26, 2002	Aug 24, 2003	252	7.24	0.26
Average			216	9.22	0.31
Median			154		

Patients were admitted between July 12, 1988, and November 12, 2003. Data are as of June 10, 2005.

a. Indicates actual days on intravenous treatment. The time from start to stop date is not necessarily the same as the days on treatment because of short periods of discontinuation (A101).

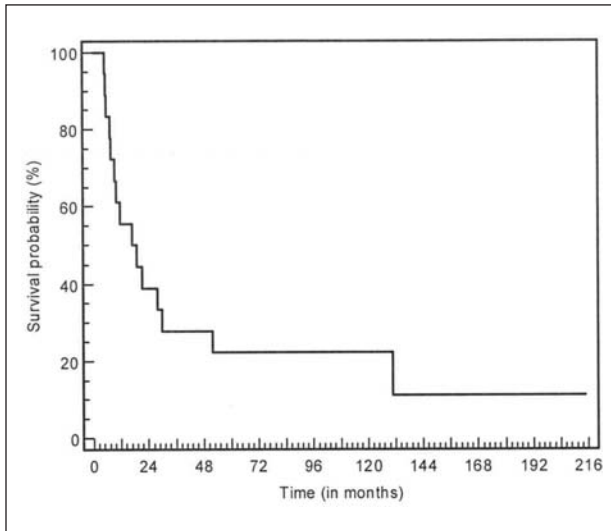


Figure 2 Overall survival from diagnosis of patients with high-grade, recurrent, and progressive brainstem gliomas treated with antineoplastons.

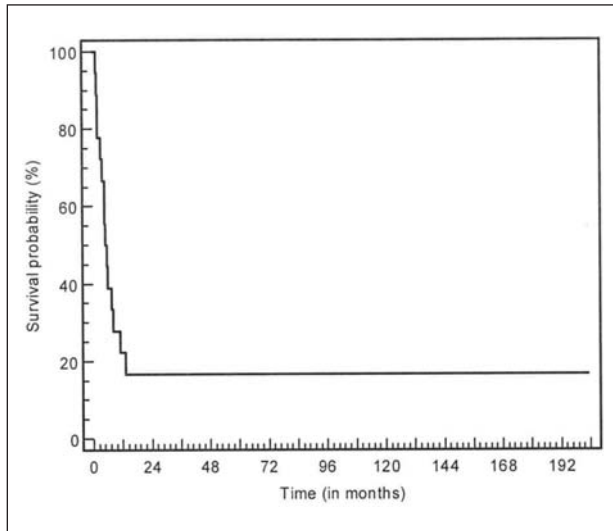


Figure 3 Progression-free survival of patients with high-grade, recurrent, and progressive brainstem gliomas treated with antineoplastons.

**Results**

**Treatment Administered**

ANP was given by intravenous injections in escalating doses to prevent peritumoral edema. Table 3 shows a summary of treatment data.

**Response Rate**

Complete responses were observed in 2 cases (11%), partial responses in 2 cases (11%), stable disease in 7 cases (39%), and progressive disease in 7 cases (39%).

**Survival Data**

Overall survival at 2 years was 39% and at 5 years was 22%. The maximum survival is approaching 18 years for a patient with recurrent, diffuse, intrinsic anaplastic astrocytoma and is more than 6 years for a patient with recurrent, diffuse, intrinsic GBM (Figure 2).

Progression-free survival at 6 months was 39% (Figure 3).

A summary of the results of treatment is shown in Table 4.

**Table 4. Summary of Results of Treatment With Antineoplastons**

Case	Response	Radiological PD <sup>a</sup>	PFS, mo	Status	KPS Baseline	KPS Follow-up	Reason for Withdrawal	OSD, mo	OST, mo
1	CR	NR	203.19	A	60	90	CR	214.7	203.2
2	PD	Sep 17, 1998	1.15	F	80	90	PD	5.2	4.3
3	PD	Mar 5, 2004	3.75	E	60	50	PD	7.7	6.3
4	SD	NR	68.09	A	40	40	N	89.3	68.1
5	SD	NR	5.82	E	80	70	N	51.9	5.8
6	SD	Jun 27, 1996	4.87	E	80	90	PD	7.2	6.5
7	PD	June 9, 1997	1.74	E	90	90	PD	5.6	3.7
8	SD	NR	13.03	E	50	100	W	18.9	13.0
9	PD	May 7, 1999	1.88	D	50	50	D	16.9	6.4
10	SD	NR	8.26	F	40	50	N	130.8	8.3
11	PR	Nov 30, 1999	7.37	D	50	80	D	11.5	11.0
12	CR	NR	68.42	A	50	90	CR	72.3	68.4
13	SD	NR	5.69	E	50	50	W	29.7	5.7
14	SD	Aug 16, 2001	4.8	F	60	60	PD	21.3	20.2
15	PD	May 18, 2001	1.68	E	50	60	PD	5.1	2.6
16	PD	Dec 27, 2002	4.67	F	50	60	PD	10.0	5.8
17	PD	NR	3.09	F	50	40	PD	9.4	3.1
18	PR	NR	10.92	D	40	40	D	27.8	10.9
		Median	5.28		50	65			

Patients were admitted between July 12, 1998, and November 12, 2003. Data are as of June 10, 2005. PD = progressive disease; PFS = progression-free survival; KPS = Karnofsky Performance Status; OSD = overall survival from diagnosis; OST = overall survival from start of antineoplastons; CR = complete response; NR = not recurrent; A = alive; F = died more than 30 days after treatment; E = died within 30 days after treatment; PR = partial response; SD = stable disease; N = patient request; W = worsening; D = died on treatment.  
a. A radiological PD on/after antineoplaston treatment.

Three patients are alive and tumor free at present. The deaths of 12 patients were most likely tumor related. There was a single death due to a pulmonary embolism and 2 cases of death possibly resulting from aspiration pneumonia.

**Toxicity**

Among the patients treated, there was 1 case of grade 4 and 2 cases of grade 3 toxicities, which consisted of reversible anemia. Generally, the treatment was well tolerated and was free from chronic toxicities.

**Case Report**

The case of patient 12 is of special interest because it represents successful treatment of a patient with recurrent, diffuse, intrinsic GBM.<sup>9</sup> Patient 12, a 40-year-old man diagnosed with GBM of the brainstem in May 1999, underwent subtotal tumor resection and standard radiation therapy. Subsequent MRI and PET scans documented tumor recurrence. Two months after completion of radiation therapy, he started ANP, which was administered over 650 days with the exception of a few short interruptions. The maximum dosage of A10 was 8.15 g/kg/d and of AS2-1 was 0.35 g/kg/d. Complete response was documented after approximately 1 year of treatment. He continues to be tumor free more than 5 years from the start of ANP therapy (Figure 4).

**Discussion**

Patients with newly diagnosed diffuse, intrinsic BSG are treated with standard radiation therapy.<sup>3</sup> Chemo-

therapy has not shown any significant value.<sup>4-6,16</sup>

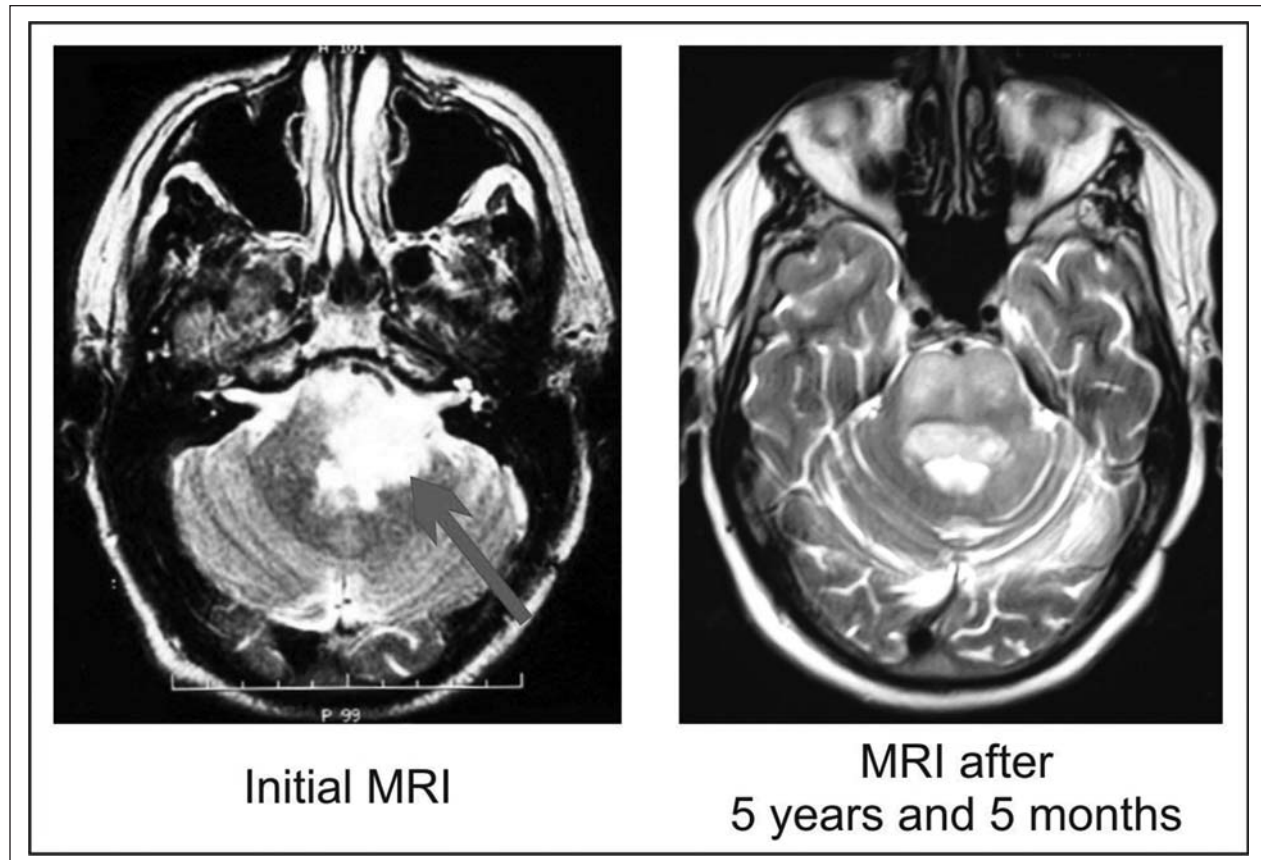
Hyperfractionation of radiation therapy has not improved treatment results and may contribute to increased toxicity and reduced patient survival.<sup>3,17</sup>

Numerous combination regimens of radiation and chemotherapy have been tried in which chemotherapeutic agents were administered before, concomitantly, or after radiation therapy.<sup>16</sup> None of these regimens, including high-dose chemotherapy with autologous bone marrow transplantation, realized an increased efficacy compared to radiotherapy alone.<sup>18,19</sup>

The introduction of temozolomide raised hopes that this agent would be more effective, but it failed to produce better responses than older regimens.<sup>6,20</sup>

Antiangiogenic therapy with thalidomide as a single agent and in combination with temozolomide, carboplatin, and radiation therapy in recurrent GBM did not produce substantially better results as well as targeted therapy with imatinib mesylate, gefitinib, and erlotinib.<sup>21-28</sup> There are no reports on the efficacy of these agents in BSG, but poor results in the treatment of recurrent high-grade gliomas do not suggest efficacy in the more difficult to treat brainstem tumors.

The overall prognosis is especially disappointing in the treatment of patients with recurrent BSG in which administration of temozolomide failed to produce significant responses with no other reports of efficacy.<sup>6</sup> There is general consensus that more than 90% of patients newly diagnosed with diffuse, intrinsic BSG will die within 2 years and patients with recurrent tumors within 6 months, despite administration of available treatment.<sup>3,4</sup> Clearly, a completely different treatment



**Figure 4** Treatment with antineoplastons (ANPs) of glioblastoma multiforme of the brainstem in a 40-year-old man (patient 12). The tumor recurred after partial resection and radiation therapy. Magnetic resonance image (MRI) before and more than 5 years after the start of treatment (T2-weighted images). The image on the left side shows a large tumor that progressed after radiation therapy and prior to ANP treatment, and the image on the right side shows resolution of the tumor 5 years and 5 months later, after administration of ANP. The results were confirmed by positron emission tomography scan.

approach is necessary.<sup>29</sup> Eradication of inoperable brain tumors requires elimination of neoplastic stem cells, which resemble normal stem cells.<sup>30</sup> This cannot be accomplished without inducing irreversible damage to the brain by radiation therapy and cytotoxic chemotherapy. New forms of therapy that affect single targets are unlikely to control the disease because they will need to affect an extremely complex network of numerous genes, proteins, and small molecules. It is our contention that successful treatment of HBSG requires multitargeted therapy such as ANP. Because of selective mechanisms that affect neoplastic cells but do not impair the function of normal cells, ANP therapy is very well tolerated and associated only with sporadic and reversible cases of acute toxicity. Overall survival from diagnosis may be artificially extended in some of our patients because of time spent for prestudy chemotherapy, radiation therapy, and surgery; however, overall survival from treatment start still remains significant considering the advanced clinical condition and stage of disease of our patients.<sup>31</sup> The absence of chronic toxicity allows

continuation of ANP until all neoplastic cells, including neoplastic stem cells, are eliminated.

### Conclusion

HBSG creates one of the most difficult problems for neurooncologists to treat. Standard radiation therapy remains the main treatment of newly diagnosed tumors, but less than 10% of patients will survive 2 years. There are no established therapies for recurrent HBSG, including temozolomide and single targeted therapies. Despite administration of available treatments, it is not expected that these patients will survive longer than 6 months.

The treatment of a small group of 18 patients reported in this article indicates that it is possible to obtain a significant response rate and long-term responses in excess of 5 years in patients with HBSG. The proposed mechanism of action of ANP is via multiple targets involved in the formation of HBSG, including the AKT/PTEN, RAS, p53, p21, MYCC, and apoptosis pathways. A low percentage of acute toxicity and a lack of chronic toxicity allow continuation of

ANP until durable objective responses are accomplished. Because a small number of patients have been evaluated, a larger study is required to confirm these results.

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