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Study of Multicentric Glioma

Phase II Study of Antineoplaston A10 and AS2-1 in Children with Recurrent and Progressive Multicentric Glioma

A Preliminary Report

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Abstract

Objective: To evaluate the response rates, survival and toxicity of treatment with antineoplaston A10 and AS2-1 (ANP) in the first 12 children enrolled in our studies diagnosed with incurable recurrent and progressive multicentric glioma.

Patients and methods: The patients' median age was 9 years. Six patients were diagnosed with pilocytic astrocytoma, four with low-grade astrocytoma and one with astrocytoma grade 2. In one case of visual pathway glioma, a biopsy was not performed due to a dangerous location. Patients received ANP intravenously initially and subsequently orally. The average duration of intravenous ANP therapy was 16 months and the average dosage of A10 was 7.95 g/kg/day and of AS2-1 was 0.33 g/kg/day. The average duration of oral ANP was 19 months and the average dosage of A10 and AS2-1 was 0.28 g/kg/day. Responses were assessed by MRI according to the National Cancer Institute's criteria and confirmed by PET scans in some cases.

Results: Complete response was accomplished in 33%, partial response in 25%, and stable disease in 33% of patients, and there was no progressive disease. One patient was non-evaluable due to only 4 weeks of ANP and lack of follow-up scans. One patient who had stable disease discontinued ANP against medical advice and died 4.5 years later. Ten patients are alive and well from 2 to >14 years post-diagnosis. Only one case of serious toxicity of reversible tinnitus, of one day's duration, was described. The study continues with accrual of additional patients.

Conclusion: The results of the present study are favourable in comparison with radiation therapy and chemotherapy. We believe that confirmation of these results through further studies may introduce a new promising treatment for incurable paediatric brain tumours.

Antineoplaston A10 and AS2-1 (ANP) are synthetic analogues of naturally occurring phenylacetylglutamine (PG), phenylacetylisoglutamine (isoPG), and phenylacetate (PN).^[1] Preclinical activity *in vitro* and *in vivo* as well as toxicology have been described in a number of publications.^[2,3] ANP has shown minimal toxicity in humans.^[4,5] Phase II clinical trials revealed an interesting spectrum of activity of ANP including astrocytoma, high-grade glioma, brainstem glioma, hormonally refractory adenocarcinoma of the prostate, adenocarcinoma of the colon with liver metastases, and hepatocellular carcinoma.^[11,6-13] Some patients (not included in this report) who responded to ANP in previously published trials had multicentric glioma (MCG).^[7,9] Good results with ANP in such cases prompted us to study ANP in children with recurrent and progressive MCG. The purpose of these studies is to determine the response rates, survival and toxicity of antineoplaston A10 and AS2-1 in children diagnosed with incurable recurrent, progressive MCG.

The first 12 children enrolled in our studies are presented in this paper. The response rates will be determined from the proportion of patients who experienced an objective tumour response (complete and partial responses [CR and PR]). A combination of A10 and AS2-1 was used based on previous observations^[1] that the combination provided better results than when each formulation was used individually.

Patients and Methods

Patient Eligibility

Patients were required to have a normal total serum bilirubin and creatinine, aspartate (AST) and alanine aminotransferase (ALT) not higher than five times the upper limit of normal, leucocyte count of 2000/mm³ or higher, and a platelet count above 50 000/mm³. Patients were both male and female and had to have a life expectancy of at least 2 months. At least 8 weeks must have elapsed since the last dose of radiation therapy and at least 4 weeks since the last dose of chemotherapy (6 weeks for nitrosoureas). Patients who were receiving corti-

costeroids were on a fixed dose for at least 1 week prior to their baseline scan.

Patients were excluded from accrual to the studies as a result of serious active infection, fever or any other serious disease that would interfere with evaluation including severe cardiac, pulmonary, hepatic or renal diseases. Patients with hypertension were excluded from accrual to the studies unless blood pressure was adequately controlled. Table I shows a summary of patient characteristics.

Patient Assessments

Initial evaluation of the patients was performed within 7 days prior to the first dose of ANP and included a complete medical history, physical examination, complete blood count and differential, prothrombin and partial thromboplastin times, a biochemical profile that included blood urea nitrogen, creatinine, uric acid, electrolytes, glucose and liver

Table I. Summary of study patients' characteristics (n = 12) as of 1 March 2004 (patients admitted between 31 July 1996 and 3 April 2002)

Characteristic	No.	%
Gender		
Male	6	50
Female	6	50
Age		
Range	9 months to 17 years	
Median	9 years	
Tumour histology		
Astrocytoma, low grade	4	34
Astrocytoma, grade 2	1	8
Pilocytic astrocytoma	6	50
No biopsy (visual pathway glioma)	1	8
Tumour size (total of measured lesions)		
Median	8.97cm ²	
Previous therapies		
Surgery	4	34
Surgery and chemotherapy	4	34
Surgery, chemotherapy and radiation	1	8
Chemotherapy only	1	8
Chemotherapy and radiation	1	8
None	1	8
Karnofsky performance status		
Range	40-100	
Median	75	

function tests, antiepileptic levels, urinalysis and a baseline MRI. Pathologists not associated with the Burzynski Clinic (BC) confirmed the histopathological diagnoses.

Treatment

For the first 3 weeks, the patients received ANP at the BC. Caretakers underwent training in catheter care and programming of the infusion pump and were not permitted to return home until they were sufficiently trained. Periodically the patient underwent a history and physical examination and laboratory tests as required by the protocol. The Co-Investigator who signed the US FDA Form 1572 submitted the patient's evaluations to the Principal Investigator and performed the patient's local care between visits to the BC. All patients (or legal guardians if a patient was incapacitated or a minor) signed the Informed Consent Form that had been previously reviewed by the FDA and the Institutional Review Board (IRB) of the Burzynski Research Institute. The study was supervised by our IRB and the membership of the IRB was in compliance with the FDA guidelines.

Daily intravenous injections of A10 (300 mg/mL) and AS2-1 (80 mg/mL) were administered through a subclavian venous catheter. Gradually escalating doses were administered by intermittent bolus injections (six times a day) using a portable Provider 6000 dual channel pump (Abbott Laboratories, North Chicago, IL, USA). Gradual dose escalation was necessary to prevent peritumoral oedema. Intravenous injections were discontinued after determination of CR, PR or stable disease (SD). After discontinuation of injections, the patients continued A10 and AS2-1 in 0.5g capsules.

Details of the criteria for the timing of dose escalation, the increments in which such dose escalations occurred, and patients' evaluations were the same as in the protocol for brain stem glioma and have been recently described in detail.^[10]

Assessment of Treatment Efficacy

MRI assessed responses according to National Cancer Institute (NCI) criteria. Positron emission

tomography (PET) scans were used to confirm CR for tumours that displayed hypermetabolism (cases 8 and 10).

Response criteria were:

Complete response (CR): Complete disappearance of all contrast-enhanced tumour(s) on imaging studies for at least 4 weeks and receiving no corticosteroids.

Partial response (PR): >50% reduction in the sum of the products of the greatest perpendicular diameters of the contrast-enhanced tumour(s) for at least 4 weeks with no appearance of new lesions on a decreasing or stable dose of corticosteroids.

Stable disease (SD): <50% change (either greater or smaller) in the sum of the products of the greatest perpendicular diameters of the contrast-enhanced tumour(s) for a minimum of 12 weeks on a stable or decreasing dose of corticosteroids.

Progressive disease (PD): >50% increase in the sum of the products of the greatest perpendicular diameters of the contrast-enhanced tumour(s) compared with nadir evaluation or appearance of new lesions.

In all cases the responses were confirmed by radiologists not affiliated with the BC. Radiologists and oncologists from the FDA evaluated the films and medical records of patients who obtained a CR and a PR. Survival time, progression-free survival (PFS), and Karnofsky Performance Status (KPS) were evaluated in addition to the response criteria, based on objective tumour measurements. PFS was measured from the start date of ANP to the date of PD, death or the last evaluation.

Protocol Design and Statistics

The design of a two-stage phase II trial recommended by Fleming was used.^[14] The FDA-reviewed protocols of the same design for children with low-grade astrocytoma (protocol BT-13) and children with visual pathway gliomas (protocol BT-23) were considered the source of all cases described in this article. The patients were selected based on the following criteria: progressive (without prior treatment) MCG or recurrent (progressive after prior treatment) MCG previously treated with sur-

Table II. Individual patient characteristics as of 1 March 2004 (patients admitted between 31 July 1996 and 3 April 2002)

Case	Age at admission (y)	Sex	Ethnicity	Date of initial diagnosis (dd/mm/yy)	Pathology code	VPG	KPS baseline	Previous treatment			Multicentric tumour location
								SU	CH	RA	
1	8	F	W	15/03/90	PA	Yes	100	SU			1. Midline suprasellar 2. Spine
2	9	F	W	30/09/96	AGII	No	90	SU			1. Left superior cerebellar peduncle 2. Left lateral portion to third ventricle 3. Lateral thalamus 4. Mid-thalamus 5. Left portion to third ventricle 6. Anterior thalamus 7. Left superior thalamus
3	15	M	L	22/05/90	ALG	No	60	SU	CH	RA	1. Medulla oblongata 2. Cervical spinal cord C1-C6
4	9	M	W	25/04/97	ALG	Yes	60	SU			1. Left suprasellar 2. Floor of the third ventricle 3. Suprasellar cistern 4. Left optic nerve and chiasma
5	17	M	I	23/03/01	ALG	No	40	SU	CH		1. Fourth ventricle and vermis 2. Spinal cord L2 3. Spinal cord L3 4. Leptomeningeal spread
6	16	M	Y	17/09/97	PA	No	50	Bx only			1. Right lateral ventricle 2. Left lateral ventricle 3. Pineal region 4. Spine (thecal sac)
7	4	F	W	22/09/95	PA	Yes	60	SU	CH		1. Optic chiasm 2. Left optic tract 3. Intraorbital cavity 4. Thalamus
8	4	F	W	24/02/95	ALG	Yes	80	SU	CH		1. Bilateral optic nerve and chiasm 2. Posterior internal capsule 3. Right cerebral peduncle

Continued next page

Table II. Contd

Case	Age at admission (y)	Sex	Ethnicity	Date of initial diagnosis (dd/mm/yy)	Pathology code	VPG	KPS baseline	Previous treatment			Multicentric tumour location
								SU	CH	RA	
9	16	M	W	15/02/90	NP	Yes	80		CH	RA	4. Right thalamus 1. Optic chiasm 2. Right optic radiation 3. Right parietal lobe 4. Corpus callosum 5. Spinal cord L2 6. Leptomeningeal spread
10	6	F	W	15/01099	PA	Yes	70	SU			1. Thalamus 2. Pons 3. Right suprasellar 4. Right basal ganglia 5. Left temporal
11	0.8	M	W	13/03/00	PA	Yes	90	SU	CH		1. Optic chiasm 2. Right optic tract 3. Left optic tract
12	16	F	W	7/04/00	PA	Yes	80	Bx only	CH		1. Optic chiasm 2. Right cerebral peduncle 3. Left cerebral peduncle 4. Internal capsule

AGII = astrocytoma grade II; **ALG** = astrocytoma, low grade; **Bx** = biopsy; **CH** = chemotherapy; **F** = female; **I** = Asian Indian; **KPS** = Karnofsky Performance Status; **L** = Latin American; **M** = male; **NP** = not performed; **PA** = pilocytic astrocytoma; **RA** = radiation; **SU** = surgery; **VPG** = visual pathway glioma; **W** = Caucasian; **Y** = Oriental.

Table III. Summary of treatment data with antineoplaston (A10 and AS2-1) therapy as of 1 March 2004 (patients admitted between 31 July 1996 and 3 April 2002)

Case	Start date (dd/mm/yy)	Stop date (dd/mm/yy)	Days on treatment IV ^a	Days on treatment PO ^a	Average dosage (g/kg/day)			
					IV treatment		PO treatment	
					A10	AS2-1	A10	AS2-1
1	31/07/96	+	1029	1676+	7.02	0.38	0.26	0.26
2	26/11/96	9/11/99	838	114	6.78	0.33	0.14	0.14
3	16/10/97	+	652	1637+	6.59	0.18	0.17	0.17
4	17/10/97	14/04/98	160		12.06	0.53		
5 ^b	3/04/02	10/01/03	262		4.99	0.29		
6 ^b	5/11/97	7/04/03	1485	425	6.32	0.21	0.17	0.17
7	18/02/98	+	154	1802+	6.51	0.38	0.33	0.33
8	20/01/99	15/02/03	224	1213	8.37	0.37	0.47	0.47
9	6/04/99	5/05/99	29		5.5	0.22		
10	11/11/99	14/4/03	228	964	12.45	0.47	0.39	0.39
11 ^b	10/05/00	10/12/01	535		10.5	0.38		
12	1/12/00	15/10/01	126	158	8.29	0.26	0.27	0.27
Average			477	575	7.95	0.33	0.28	0.28

a Indicates actual days on treatment. The time from start to stop date is not necessarily the same as the days on treatment, due to short periods of discontinuations.

b Cases: 5, 6 and 11 were treated under Special Exceptions granted by the US FDA.

IV = intravenous; PO = oral; + indicates ongoing oral antineoplaston therapy.

gery, radiation therapy and/or chemotherapy. Response rates, survival statistics, incidences of adverse events, maximum dosages, average dosages, duration of treatment and summary of patients' statistics were obtained using Microsoft Excel 97 and Access 02. A biostatistician reviewed survival data.

Results

Accrual and Patient Characteristics

This report describes the results of ANP administration in the first 12 patients diagnosed with recurrent or progressive MCG enrolled in the studies under FDA and IRB supervision, between July 1996 and April 2002. There is ongoing accrual of new patients. Table II shows individual patient characteristics.

Toxicity

ANP was tolerated very well with only one case of serious (grade 3 by NCI criteria) toxicity of reversible bilateral tinnitus and mild (grade 2) toxicities of anaemia, nausea, vomiting, skin rash and

somnolence. After development of tinnitus the patient was referred to the hospital, and because of the hospital referral this event was classified as a grade 3 toxicity. Hospitalisation was not necessary and the tinnitus resolved completely within 12h.

Efficacy

The average duration of intravenous ANP was 16 months and the average dosage of A10 was 7.95 g/kg/day and of AS2-1 was 0.33 g/kg/day. The average duration of oral ANP was 19 months and the average dosage of A10 and AS2-1 was 0.28 g/kg/day. Table III shows a summary of treatment data.

One patient was non-evaluable due to only receiving 4 weeks of ANP and lack of follow-up scans. This patient died while receiving ANP due to a non-haemorrhaging brain infarction and was considered a treatment failure. Complete responses were observed in four patients (33%), partial responses in three patients (25%), and stable disease in four patients (33%). There were no cases of progressive disease. One patient who had SD discontinued ANP against medical advice and died 4.5 years later. Ten patients are alive and well from 2 to >14 years

Table IV Summary of results of treatment with antineoplastic therapy as of 1 March 2004 (patients admitted between 31 July 1996 and 3 April 2002)

Case	Response	Max. response date (dd/mm/yy)	Time to max. response (mo)	Radiological PD as of 1/03/04	PFS (y)	Status	KPS baseline	KPS follow-up	Reason for withdrawal	Survival time from diagnosis (y)
1	CR	20/09/02	74.2	No PD	7.8	A	100	100	C	14.2
2	PR	20/08/99	33.0	No PD	7.1	A	90	100	N	7.2
3	PR	17/03/00	29.2	No PD	6.6	A	60	90	C	14.0
4	SD	12/01/98	2.9	No PD	5.0	D1	60	80	N	5.5
5	SD	22/08/02	4.7	No PD	1.0	A	40	40	N	2.0
6	CR	18/03/99	16.5	No PD	6.5	A	50	100	CR	6.6
7	SD	2/07/98	4.4	No PD	6.2	A	60	90	C	8.6
8	CR	17/01/03	48.3	No PD	4.9	A	80	80	CR	8.8
9	NE	NE	NE	NE	NE	D2	80	80	W	9.2
10	CR	25/06/03	43.8	No PD	4.4	A	70	100	N	4.5
11	PR	15/06/01	13.3	No PD	2.6	A	90	90	N	2.8
12	SD	20/04/01	4.6	No PD	3.2	A	80	80	N	3.8
Median			16.5		5.0		75.0	90.0		6.9

A = alive; **C** = current; **CR** = complete response; **D1** = died after 4.5 years from discontinuation of antineoplastic therapy; **D2** = died after 4 weeks of treatment; **KPS** = Karnofsky Performance Status; **N** = patient request; **NE** = non-evaluable; **PD** = progressive disease; **PFS** = progression-free survival (the same as overall survival from the start of antineoplastic therapy); **PR** = partial response; **SD** = stable disease; **W** = worsening of clinical condition.

post-diagnosis and three patients continue oral ANP. Table IV summarises ANP responses, baseline and current status, overall survival, and PFS.

Figure 1 shows a decrease of the tumour size in a 4-year-old girl (case 8), who developed left-sided weakness, difficulty walking, visual changes, imbalance and speech difficulties at the end of 1994. On 17 February 1995, she underwent right parietal craniotomy with partial resection of the brain tumour. Pathology confirmed low-grade desmoplastic astrocytoma of infancy. She received 13 treatments of carboplatin. After initial decrease of the tumour size (documented in December 1995), her disease progressed in December 1998. She received ANP from 20 January 1999 to 15 September 2002. The treatment was discontinued after CR, which was confirmed by MRI and PET scan.

Figure 2 shows the response to ANP in a 6-year-old girl (case 10). The patient developed the first signs and symptoms of the disease in the summer of 1999 consisting of blurring of the optic disc and decreased vision. Her symptoms progressed in September 1999 and she was found to have optic nerve atrophy. In October 1999, she was diagnosed with multicentric pilocytic astrocytoma. Her surgical intervention was limited to a biopsy. ANP was begun in November 1999 and resulted in CR, as confirmed by PET scan. She is presently free from tumour and in good health (KPS = 100).

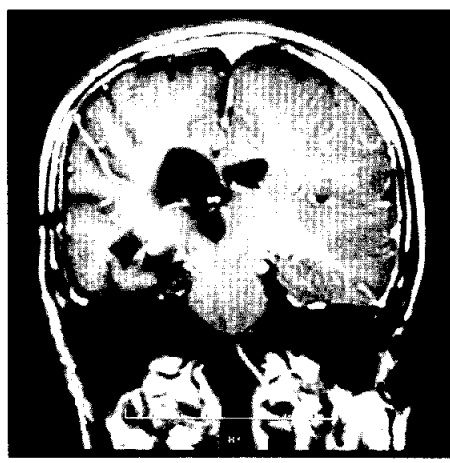
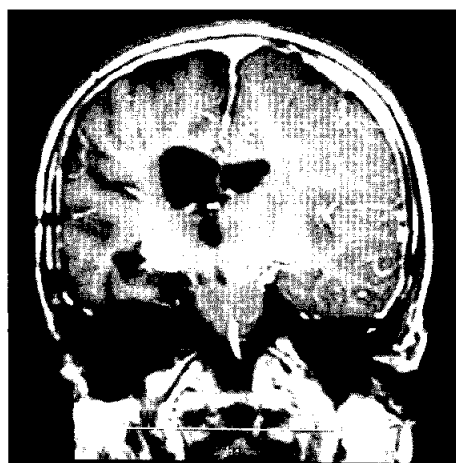
Survival

Of the 12 patients with MCGs treated with ANP, ten are currently alive and two have expired. Survival probability estimates by the Kaplan-Meier method are shown in figure 3.

One patient died due to a non-haemorrhagic brain infarction only 4 weeks after initiation of ANP and another patient who had discontinued ANP against medical advice, died 4.5 years later. There was no evidence that these were treatment-related deaths. The median survival post-diagnosis was approximately 7 years and from initiation of ANP was 5 years with studies still ongoing. Median PFS was also 5 years and was the same as overall survival from the start of ANP.



Baseline – 14 January 1999



On treatment – 29 January 2003

Fig. 1. Recurrent multicentric glioma in a 4-year-old female (case 8). T1-weighted gadolinium-enhanced magnetic resonance images (MRIs) of the head show reduction and subsequent disappearance of the lesions during treatment with antineoplaston A10 and AS2-1. The residual changes visible on the MRIs did not correspond to active hypermetabolic tumour, as confirmed by positron emission tomography (PET) scan.

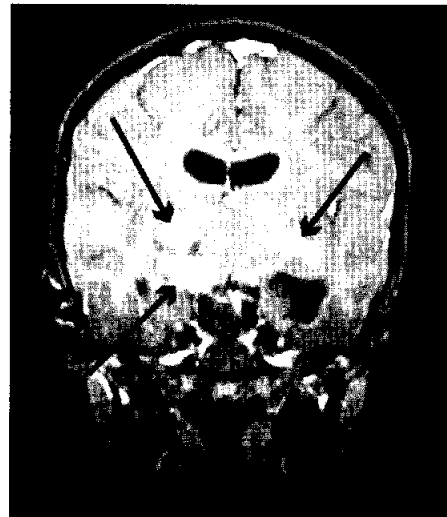
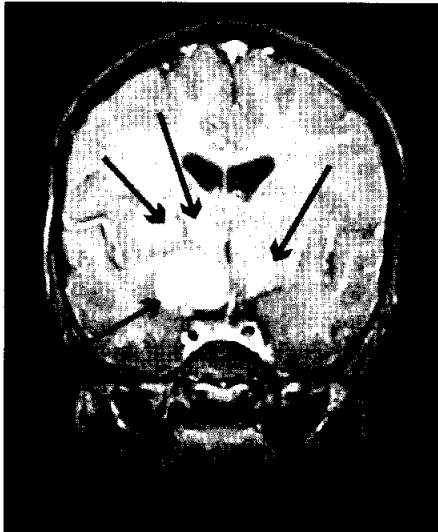
Discussion

Controversy still surrounds the pathogenesis of MCGs. According to an earlier theory presented in 1959, the multicentric nodules originate from a wide field of neoplastic transformation, which may involve the entire brain. A progressive proliferation within such a field will produce the lesions occur-

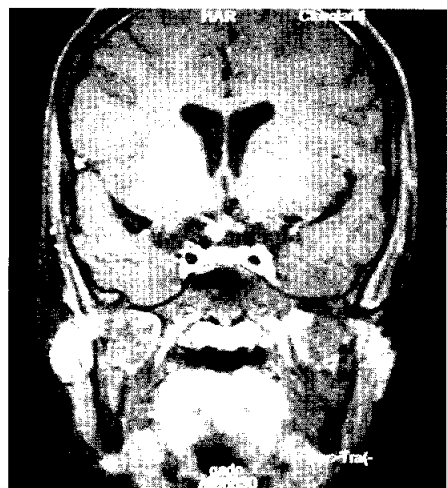
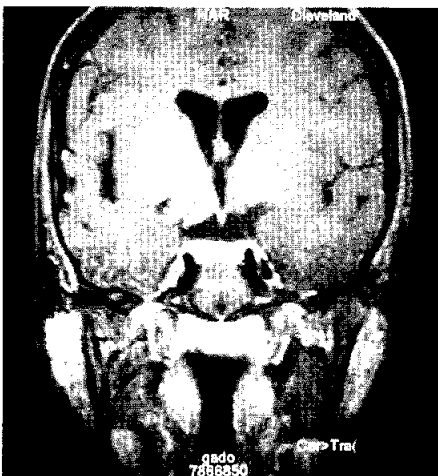
ring simultaneously at multiple sites. Various biochemical, hormonal or even mechanical factors may trigger this process.^[15] High-grade tumour does not necessarily correlate with multicentricity. As a matter of fact, low-grade astrocytomas are often implicated in such lesions.^[16] In gliomas, in addition to the tumour core, there are numerous invasive single cells, which can be detected several centimetres

from the core. Tumour location is also associated with the development of MCGs in patients with PA. Patients with PA of the hypothalamic region were 23 times more likely to develop multicentric spread than those with non-hypothalamic tumours.¹¹⁷ Recent advances in molecular genetics offer a better

explanation of crucial events in the formation of MCGs. In high-grade gliomas, there is substantial evidence of accumulative genetic alterations, which occur less frequently in low-grade gliomas. Formation of an astrocytoma is not definitely associated with mutations of the *TP53* gene.¹¹⁸ Likewise, *RAS*



Baseline – 18 November 1999



On treatment 18 October 2002

Fig. 2. Progressive multicentric glioma in a 6-year-old female (case 10). T1-weighted gadolinium-enhanced magnetic resonance images (MRIs) of the head show reduction and subsequent disappearance of the lesions during treatment with antineoplaston A10 and AS2-1. The residual changes visible on the MRIs did not correspond to active hypermetabolic tumour, as confirmed by positron emission tomography (PET) scan.

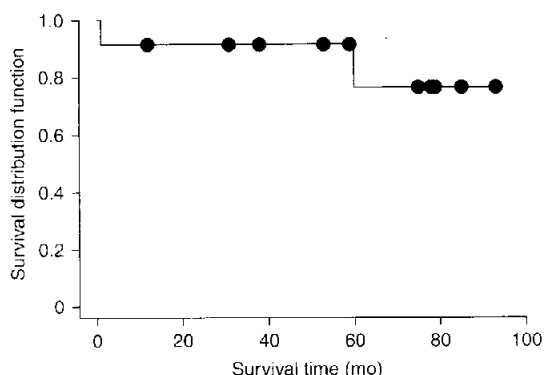


Fig. 3. Kaplan-Meier survival probability estimates from the start of treatment with antineoplaston A10 and AS2-1 ($n = 12$).

oncogene mutations, which occur in approximately 30% of all cancers, have not been identified in human astrocytomas.^[19] New methods can detect more subtle epigenetic events involved in the silencing of tumour suppressor genes in astrocytomas. The most important mechanism is methylation of promoter sequences of the tumour suppressor genes and deacetylation of the histones.^[20,21] Such changes may result in the functional loss of the *TP53*, *p21* and *NF1* tumour suppressor genes. In the absence of a *RAS* mutation, promotion of neoplastic growth in an astrocytoma occurs through the *p21 RAS* protein, which can be activated through the growth factor-receptor tyrosine kinase (GF-RTK)-*RAS* pathway and loss of the *NF1* gene.^[22] In addition to silencing of tumour suppressor genes through hypermethylation of promoter sequences, genome-wide hypomethylation of repetitive sequences effects genomic stability and contributes to amplification of oncogenes and silencing of tumour suppressor genes.^[23,24] A recently proposed mechanism suggests that RNAi could silence a normally expressed gene.^[25] According to this mechanism, hypomethylated repetitive sequences generate dsRNA, which is cleaved by Dicer to give siRNA. After hybridisation with DNA of repetitive sequences, siRNA triggers a cascade of events leading to the formation of heterochromatin and silencing of nearby genes.

To summarise, epigenetic mechanisms involving the tumour suppressor genes *TP53*, *p21* and *NF1* and the *RAS* oncogene pathway (GF-RTK-*RAS*)

cause astrocytoma cells to become invasive and resistant to conventional therapies. The natural ability of astrocytes to migrate extensively during development may explain their ability to form multicentric lesions. All these factors may therefore affect the number of cases we classify as MCGs. The natural history of MCG is responsible for the failure of conventional approaches including surgery, radiation therapy and cytotoxic chemotherapy. Limitation of the spread of the disease by surgical intervention is of little value since even a massive resection cannot eradicate the tumour. The cells in MCG activate a migratory phenotype and temporarily lower their proliferation rate, rendering them relatively resistant to radiation therapy and cytotoxic chemotherapy.^[16] Therefore, therapies exploring epigenetic mechanisms seem to be more efficacious. The components of ANP, PN and PG exploit such mechanisms.^[26-33] PN interrupts signal transduction in the *RAS* pathway through the inhibition of farnesylation of the *RAS* protein and activates the *TP53* and *p21* genes through demethylation of their promoter sequences.^[29,30] PN also activates the *p21* gene through the inhibition of histone deacetylase, which has a synergistic effect with the inhibition of methyltransferase.^[31,33] PG normalises the methylation of the repetitive sequences of these genes, inhibiting amplification of oncogenes and silencing of tumour suppressor genes through an RNAi mechanism. In addition, PG decreases expression of the oncogene *AKT2* and the transforming growth factor $\beta 1$ (*TGF β 1*).^[32,33] PG enters human glioma cells (U87) via the stereospecific amino acid transporters and inhibits the uptake of the growth-critical amino acids L-glutamine and L-leucine.^[32,33] The components of ANP effect oncogene and tumour suppressor gene pathways and the nutritional requirements of neoplastic cells. It is not yet known, however, if the mechanisms identified in cell cultures correspond to processes involved in tumour responses in patients treated with ANP.

The available literature provides limited information on the treatment options of MCG. Mamelak et al. reported the results of treatment of 11 patients.^[17] Eight of these patients were treated with various

chemotherapy regimens; one with radiation therapy and chemotherapy, one with radiation therapy alone and another one received no treatment. Remission (their definition of remission was not provided) was documented in two patients (18%), SD in five patients (46%) and four patients died (36%). Three of these patients died from disease progression and one from chemotherapy-induced toxicity. A small number of additional reports refer to single cases or a small series of cases, which does not allow statistical evaluation of the results.^[34-36]

Shaw and Wisoff have extensively reviewed the results of four prospective clinical trials in adults and one in children with solitary low-grade gliomas.^[37] The most important prognostic factor was the extent of surgical resection, which is not significant in MCG. There was no difference in overall survival between patients who received radiation therapy and those not treated after surgery. Likewise, there was no difference in overall survival between groups of patients treated with radiation therapy alone versus radiation and chemotherapy with lomustine. Chamberlain and Grafe reported the results of treatment of 14 children with solitary recurrent chiasmatic hypothalamic gliomas treated with oral etoposide, and described one CR (7%), four PRs (29%), three SDs (21%) and six PDs (43%).^[38] The Pediatric Oncology Group reported a study that evaluated treatment with carboplatin for solitary progressive optic pathway tumours. Of the 50 eligible and evaluable patients, there were two PRs (4%), 37 SDs (74%), and 11 PDs (22%). Significant toxicities included neutropenia, lymphopenia, thrombocytopenia, anaemia and allergic reactions.^[39]

Conclusion

Recurrent and progressive MCGs have a poor prognosis and there are no curative standard treatments currently available. We observed good results in a small number of children with progressive MCG and recurrent MCG post-standard therapy who were subsequently treated with ANP. The majority of patients had complete or partial response, one-third had stable disease and there was no dis-

ease progression with overall relative minimal toxicity due to ANP. The patients who received adequate ANP did not experience tumour recurrence. The observation period of a maximum of approximately 8 years has been short (for this type of tumour), but preliminary results appear promising. In spite of promising response rates, this is a preliminary report only due to the small number of patients assessed. Ongoing studies are underway and will be needed for further evaluation and comments. We believe that confirmation of these results through further studies may introduce a new promising treatment for incurable paediatric brain tumours.

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