

Primary CNS Tumors and Leptomeningeal, Disseminated and/or Multicentric Disease in Children Treated in Phase II Studies with Antineoplastons A10 and AS2-1

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Abstract

It is estimated that as many as 30% of patients with primary CNS tumors have leptomeningeal, disseminated, and/or multicentric disease (LDM). These patients respond poorly to conventional therapy. Fifty-seven children with LDM (median age of 7.1 years) were treated in multiple prospective phase II clinical studies of high- and low-grade primary CNS tumors with Antineoplastons A10 and AS2-1 (ANP). Their inclusion in this analysis was based on MRI imaging. Patients with glioblastoma were excluded. The patients received ANP therapy 6 times daily; A10: 8.77 g/kg/d; AS2-1: 0.35 g/kg/d. The response to ANP was monitored by MRIs every 8 weeks. Patients evaluable for efficacy ($N = 40$) received 12 or more weeks of ANP or developed progressive disease (PD) before 12 weeks. 10 patients (17.5%) achieved an objective response (OR) with 4 (7%) achieving a complete response (CR) and 6 (10.5%) had a partial response (PR). Stable disease (SD) was maintained in 7 patients (12.3%) and PD developed in 23 patients (40.4%). Survival analysis of the 57 children showed 2- and 5-year overall survival (OS) were both 28% while 10- and 15-year OS were both 26%. One of the patients achieving an OR had atypical teratoid/rhabdoid tumor (AT/RT) while nine had low-grade gliomas (LGGs). Grade 3 and 4 toxicities included hypokalemia (14.0%); fatigue, anemia, hyponatremia and leukopenia (3.5% each); diarrhea, hypertension, joint pain, thrombocytopenia, and somnolence (1.8% each). These findings suggest the need for a single-arm, phase II study of ANP in children with LDM.

Keywords: Antineoplastons A10 and AS2-1, brain tumors in children, disseminated disease, leptomeningeal disease, multicentric disease, phase II clinical trial

1. Introduction

Leptomeningeal, disseminated and/or multicentric disease (LDM) have been associated with a poor prognosis in childhood brain tumors when compared to solitary lesions. Dissemination refers to widespread involvement with the disease of the brain and spinal cord. Leptomeningeal metastases (LM) occur when brain tumor cells spread to the membranes (meninges) covering the brain and spinal cord.

“Multiple” gliomas were first observed by Bradley in 1880 (Bradley, 1880). The criteria for multicentricity were reviewed by Takeda and Salvati (Takeda, Tanaka, Kawabuchi, & Nakajima, 1976; Salvati, Oppido, Artizzu, Fiorenza, & Orlando, 1991). The neuro-pathologist, Hans-Joachim Scherer (Scherer, 1938), described secondary structures of glioma growth along existing cytoarchitectural elements, such as neurons, white matter tracts, and blood vessels. Batzdorf and Malamud (Batzdorf, & Malamud, 1963) characterized the modes of growth in gliomas by establishing the initial criteria for distinguishing “multiple” (now referred to as multifocal) and “multicentric” gliomas. Multifocal gliomas were thought to disseminate along established CNS routes while multicentric gliomas were widely separated in location and/or time. By this definition, multifocal glioma consisted of tumors separated by white matter tracts within the same hemisphere, whereas multicentric glioma consisted of widespread tumors, such as those occurring in opposite hemispheres or separated by the tentorium.

However, the differentiation of multifocal and multicentric disease is problematic. Geer and Grossman (Geer & Grossman, 1997) suggested that interstitial fluid along white matter tracts could be a potentially important mechanism for the dissemination of glioma cells and postulated that glioma cells were inherently capable of migration along white matter tracts to distant areas of the brain. Claes and colleagues (Claes, Idema, & Wesseling, 2007) suggested that multicentric tumors were likely to develop because of the unique propensity of

glioma cells to invade normal brain and migrate long distances.

In 1936, Courville (Courville, 1936) reported that approximately 9% of all gliomas were multicentric while other investigators (Batzdorf & Malamud, 1962; Manzini & Serra, 1952; Russel & Rubinstein, 1963; Willis, 1953; Zülch, 1957) estimated the incidence to be approximately 2.5%. This discrepancy likely reflects the difficulty in differentiating multifocal and multicentric disease.

It has been reported that approximately 5% of low grade gliomas (LGGs) present with LM at the time of diagnosis and 7% - 10% of LGGs present with LM at the time of disease progression (Perilongo, Garre, & Giangaspero, 2003). The frequency of LM when categorized by the primary tumor site was as follows: cerebellum and brainstem 3%, cerebral cortex 1%, diencephalic region 7%, and spinal cord 1% (Hunkin, Siffert, Velasquez, Zagzag, & Allen, 2002).

Current treatment for children with recurrent glioma has been reviewed (S. Burzynski, Janicki, & G. Burzynski, 2014) and includes temozolomide, carboplatin, irinotecan, and targeted therapy with bevacizumab and tipifarnib.

Antineoplastons A10 and AS2-1 (ANP) are synthetic derivatives of glutamine, isoglutamine, and phenylacetic acid (Burzynski, 2004). A10 is a synthetic formulation consisting of a 4:1 ratio of phenylacetylglutamine sodium (PG) and phenylacetylisoglutamate (isoPG). AS2-1 is a synthetic formulation with a 4:1 ratio of phenylacetate sodium (PN) and PG.

The results of phase II studies of ANP therapy in children and adults with gliomas have been published (S. Burzynski, Kubove, & B. Burzynski, 1992 [Objective Response (OR) = 30.0%]; S. Burzynski, G. Burzynski, & Janicki, 2014 [OR = 13.3%; 5-year Overall Survival (OS) = 3.5%]; S. Burzynski, Janicki, & G. Burzynski, 2014 [OR = 13.3%; 5-year OS = 2.6%]; S. Burzynski, Janicki, G. Burzynski, & Marszalek, 2014, pp 565-577 [OR = 26.7%; 5-year OS = 6.7%]; S. Burzynski, Janicki, G. Burzynski, & Marszalek, 2014, pp 2051-2061 [OR = 29.4%; 5-year OS = 5.9%]; S. Burzynski, Janicki, G. Burzynski, Marszalek, & Brookman, 2014 [OR = 12.2%; 5-year OS = 4.8%]; S. Burzynski, Janicki, G. Burzynski, 2015 [OR = 18.5%; 5-year OS = 11.0%]; S. Burzynski, Janicki, G. Burzynski, & Marszalek, 2015 [OR = 21.1%; 5-year OS = 21.0%]; S. Burzynski, Janicki, G. Burzynski, & Marszalek, 2015, pp 334-344 [OR = 36.4%; 5-year OS = 73.0%]. These studies demonstrated that ANP is well-tolerated and generally contributes to more frequent objective responses and better survival than that reported with other therapeutic regimens.

In this paper, we present our review of 57 children with primary central nervous system (CNS) tumors and LDM treated with ANP therapy in phase II studies at the Burzynski Clinic (BC) in Houston, Texas.

2. Methods

2.1 Patient Population

A review of the medical records of all the patients treated in the prospective phase II clinical trials of ANP therapy at the BC, from 1993 to 2014, yielded 57 pediatric patients (age < 18 years) with primary central nervous system (CNS) tumors and LDM. The records of all children treated in prospective phase II clinical trials of Antineoplastons A10 and AS2-1 were reviewed. These phase II studies had been developed at the Burzynski Research Institute, Inc. (BRI), reviewed by the FDA, and approved by the Institutional Review Board (BRI-IRB). Of the 57 children treated in this program, 34 of these children (60%) were given permission by the FDA to be treated as compassionate exception (CE) patients since they did not meet all of the stated inclusion/exclusion criteria. CE patients received the same treatment as study patients.

All patients with primary glioblastoma multiforme (GBM) were excluded. The median Karnofsky or Lansky performance score at baseline was 60 (range 20-100).

Signed informed consent documents were obtained from the children's legal guardians before enrollment. Dr. S. R. Burzynski was principal investigator for the clinical trials and treatment was initiated at the BC.

Distribution of the primary CNS tumors by histology and location are presented in Table 1. This report examines the OR and OS rates and treatment tolerance in this group of children and presents two illustrative clinical cases of multicentric glioma.

Table 1. Distribution of primary CNS tumors by histology and location

Histology and Location	No of Patients
Diffuse intrinsic pontine glioma (DIPG)	5
Brainstem glioma (BSG)	5
Anaplastic astrocytoma (AA)	3
Anaplastic ependymoma	4
Astrocytoma, pilocytic-spine	1
Astrocytoma/astrocytoma pilocytic	6
Astrocytoma-brain-spine-disseminated	1
Atypical teratoid/rhabdoid tumor (AT/RT)	3
Choroid plexus carcinoma	2
Ependymoma	2
Ganglioglioma	1
Meningioma	1
Oligodendroglioma-spine	1
Primitive neuroectodermal tumor (PNET)	18
Optic pathway glioma (OPG)	4

2.2 Study Design

The 57 children included in this review had participated in prospective single-arm, two-stage, interventional phase II trials of ANP therapy. The sample size for each clinical trial was calculated based upon the method of Chang and colleagues (Chang, S., Kuhn, J. G., Robins, H. I., Schold, S. C., Spence, A. M., ... Prados, M.D., 1999) as described previously (Burzynski et al., 2015, pp 13-23). The primary end-point of each clinical trial was the OR rate. Every child had magnetic resonance imaging (MRI) of the brain and/or spinal column, with gadolinium enhancement, within two weeks of starting ANP therapy and every eight weeks thereafter. For all measureable (≥ 5 mm) enhancing lesions on the baseline T1-weighted MRI images, the product of the greatest perpendicular diameters was calculated and the sum of these products determined (Wen et al., 2012; Weller, Cloughesy, Perry & Wick, 2013). To identify OR to ANP therapy, this baseline sum was compared to the sum of these products as determined from the T1-weighted images, or follow-up MRIs.

No study or CE children who participated in phase II studies at BC were excluded from the initial analysis and all children who met the criteria of LDM were included in this review. Inclusion and exclusion criteria were unique to each phase II study and included patients with newly diagnosed and persistent/recurrent disease. Those with persistent/recurrent disease had undergone surgery, radiotherapy, and/or chemotherapy. Patients ≥ 18 years of age or with GBM were excluded. The high prevalence of multicentric disease in GBM necessitates separate analysis.

2.3 Administration of ANP Therapy

ANP therapy was delivered via a dual chamber infusion pump and a subclavian venous catheter (Broviac, Hickman or Groshong). The pump was programmed to infuse doses of A10 and AS2-1 given every four hours. Details of the administration of A10 and AS2-1 have been previously described (S. Burzynski, Janicki, & G. Burzynski, 2014). No other anti-cancer treatment was permitted. Each child was treated at the BC for three or more weeks and instruction in the maintenance of ANP therapy was provided to the child (as possible) and to the legal guardian. At the treating physician's discretion, and after completion of training, in the home administration of Antineoplaston therapy, each child was sent home under the supervision of a local sub-investigator. Reasons for stopping ANP therapy included patient (or legal guardian) request, worsening of a child's clinical condition, an intolerable adverse event (AE), and progressive disease (PD).

Medications that were considered necessary for the child's welfare and that did not interfere with the evaluation of tumor response to ANP therapy were given at the discretion of the child's treating physicians. Corticosteroid dosages were based on symptoms and signs of increased intracranial pressure and were adjusted, as necessary, to maintain neurologic stability.

2.4 Evaluation of Objective Response to ANP Therapy

Objective responses to ANP therapy were a complete response (CR) and a partial response (PR). A CR was defined by the disappearance of all enhancing disease on T1-weighted MRI images that was sustained for at least four weeks. The patient was off corticosteroids during this four week period or on a physiologic replacement dose to maintain neurologic stability. A PR was defined by $\geq 50\%$ decrease in the sum of the products of the greatest perpendicular diameters of all measureable enhancing lesions on T1-weighted MRI images, as compared to baseline, that was sustained for a minimum of four weeks and the patient was on stable or decreasing doses of

corticosteroids.

Cerebrospinal fluid (CSF) analysis was performed during this four week period when possible, but was not used as critical criterion in the evaluation of OR.

2.5 Evaluation of Survival

Overall survival was determined from the first day that any ANP therapy was received until death from any cause. Surviving children were censored at the date of their last follow-up and the distributions of survival were estimated by Kaplan-Meier analysis using MedCalc Statistical Software, version 14.12.0, (MedCalc Software bvba, Ostend, Belgium).

3. Results

All patients included in this review were treated in a similar fashion. Therefore, efficacy and toxicity are presented in summary fashion.

3.1 Efficacy

Excluding patients with a diagnosis of GBM, 673 patients were treated in phase II studies of ANP therapy. Of these, 312 (46.4%) were children (< 18 years). In these children, 57 cases (18.3%) of disseminated, leptomeningeal, and/or multicentric disease were identified. 10 of these 57 children achieved an OR (17.5%), 4 achieved a CR (7%) and 6 achieved a PR (10.5%). Table 2 provides summary information regarding these 10 cases.

OS was determined for the group of 57 children. On 11/23/2015, 15 surviving children (26.3%) were censored at the date of their last follow-up. Overall survival data are illustrated in Figure 1, which provides the Kaplan-Meier Survival curve. Two- and five-year overall survival were both 28% while 10- and 15-year overall survival were both 26%.

Table 3 describes the number of deaths and the number of children censored.

Table 2. Best response in ten children with CNS tumors and disseminated, leptomeningeal, and/or multicentric disease who participated in phase II clinical trials of ANP therapy and achieved an objective response

Case	Age (Years)	Patient Type	Diagnosis	Disease Type	Best Response
1	< 1	S	Visual pathway astrocytoma (pilocytic astrocytoma)	M	PR
2	4	CE	Atypical teratoid / rhabdoid tumor	L, M	CR
3	4	S	Visual pathway astrocytoma, low grade	M	PR
4	6	S	Visual pathway astrocytoma (pilocytic astrocytoma of the optic chiasm, optic tract, and hypothalamus)	M	CR
5	8	S	Ganglioglioma	M	PR
6	8	CE	Oligodendroglioma of the spinal cord	D, M	PR
7	9	S	Astrocytoma of the thalamus and brainstem, grade 2	M	PR
8	9	S	Pilocytic astrocytoma, grade 1	L, D, M	PR
9	15	S	Low grade astrocytoma	M	CR
10	16	CE	Pilocytic astrocytoma of the pineal region and spinal cord	L, D, M	CR

Note: CE-compassionate exception patient, CR-complete response, D-disseminated disease, L-leptomeningeal disease, M-multicentric disease, PR-partial response, S-study patient.

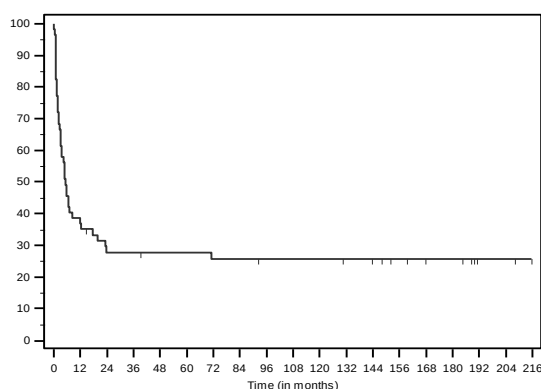


Figure 1. Kaplan-Meier survival curve for 57 children with CNS tumors and disseminated, leptomeningeal and/or multicentric disease

Table 3. Status of children on 11/23/2015, the date of Kaplan-Meier survival analysis

Number of Deceased (%)	Number Censored at Date of Last Follow-Up (%)	Number of Children in Total (%)
42 (73.7%)	15 (26.3%)	57 (100.0%)

3.2 Toxicity

All AEs were classified and graded according to CTCAE v3.0.

Grade 3 and 4 toxicities included hypokalemia (14.0%); fatigue, anemia, hyponatremia and leukopenia (3.5% each); diarrhea, hypertension, joint pain, thrombocytopenia, and somnolence (1.8% each).

4. Case Studies

4.1 Case Study

Child # 004842 was a healthy 10-year-old white female, when, in the summer of 1996, she developed a tremor of her right hand and leg. MRI evaluation at the university hospital confirmed the presence of a tumor located in the left side of the thalamus and extending to the upper brainstem. The child underwent a craniotomy with subtotal tumor resection on September 20, 1996. Histologic examination of the resected tumor specimen showed a grade 2 astrocytoma. She did not have adjuvant radiation therapy or chemotherapy. A follow-up MRI of the brain on November 8, 1996 showed progression of her disease.

The patient was evaluated at the BC and enrolled in a phase II study of ANP therapy in children with a low-grade astrocytoma (protocol BT-13), beginning treatment on November 26, 1996. Over the course of treatment, the dosage of A10 was gradually increased to 7 g/kg/d. After 250 days at that dosage, the dosage of A10 was gradually increased to 12.6 g/kg/d, which was maintained for a period of 40 days and then reduced to 7.5 g/kg/d. Over the entire course of ANP therapy, the median dose of A10 was 6.8 g/kg/d while the median dose of AS2-1 was 0.34 g/kg/d. ANP therapy was permanently discontinued on June 11, 1999, but the child continued oral formulations of A10 and AS2-1 until November 8, 1999.

On evaluation of the baseline MRI (November 8, 1996), an independent outside radiologist found the child to have seven measureable, enhancing brain and brainstem lesions. The sum of the products of the greatest perpendicular diameters of these seven lesions (SUM) was 10.88 cm². On April 8, 1997, after 5 months of ANP therapy, follow-up MRI revealed the sum of the products to be 5.22 cm², a decrease of 52% from baseline (Figure 2).

The child had achieved a PR and that PR that persisted until August 20, 1999, more than 28 months, with the greatest percent reduction in the sum of the products being 74.7%. During the time period of the PR, the child's corticosteroid dosages fell from 4 mg/d (April 8, 1997) to 2 mg/d (August 20, 1999). However, from September 2, 1997 to May 17, 1999, the child's corticosteroid dosages were ≤ 1 mg/d and from June 9, 1998 to May 17, 1999, she was not receiving corticosteroids.

Over the course of her ANP therapy, the child experienced eight Grade 1 and 2 ADEs that were possibly related to ANP therapy: 1) fatigue, 2) vomiting, 3) nausea, 4) somnolence/depressed level of consciousness, 5) blurred vision, 6) allergic reaction, 7) rigors/chills, and 8) hot flashes/flushes. All of these ADEs resolved with ANP therapy dose reduction or temporary discontinuation of ANP therapy.

The last documented contact was on October 22, 2012. At that time, the patient, age 26, had OS since the start of ANP therapy of over 19 years. She had persistent right arm tremors but had been maintaining a good quality of life with a Karnofsky performance status of 90. There had been no long-term disability or chronic toxicity related to ANP therapy. The patient had not received any additional anti-cancer therapy since ANP therapy was discontinued and had not been taking any prescription medications.

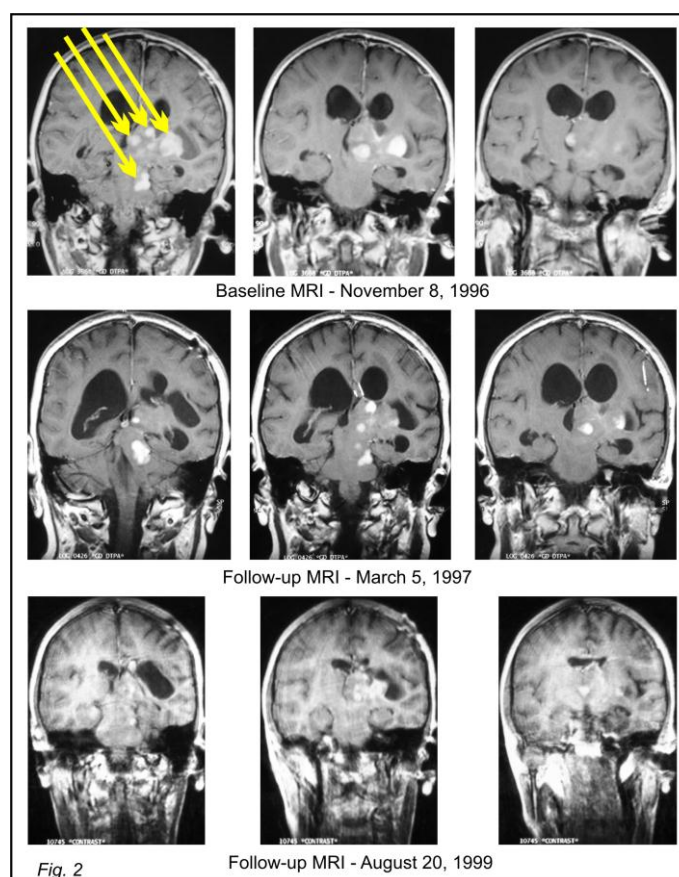


Figure 2. i) Baseline MRI (11/8/1996) showing multicentric astrocytoma, grade 2, in a 10-year-old female; ii) Follow-up MRI (3/5/1997) showing a partial response; and iii) Follow-up MRI (8/20/1999) showing persistence of the partial response.

4.2 Case Study

Child # 006252 was a healthy seven-year-old white female, when, in the summer of 1999, she developed difficulty reading. Ophthalmologic examination showed blurring of the right optic disc consistent with optic nerve atrophy. MRI evaluation at the university hospital confirmed the presence of a tumor involving the optic chiasm, hypothalamus, and left hemisphere. The child underwent stereotactic biopsy on October 13, 1999. Histologic examination of the biopsy specimen showed a pilocytic astrocytoma. She was not a candidate for tumor resection or stereotactic radiotherapy.

The patient was evaluated at the BC and enrolled in a phase II study of ANP therapy in children with visual pathway glioma (protocol BT-23), beginning treatment on November 11, 1999. The dosage of A10 was gradually increased to a maximum of 18.81 g/kg/d. Over the entire course of ANP therapy, the median dose of A10 was 10.85 g/kg/d while the median dose of AS2-1 was 0.45 g/kg/d. ANP therapy was permanently discontinued on August 22, 2000, but the child was continued on oral formulations of A10 and AS2-1 until April 14, 2004.

On evaluation of the baseline MRI (November 8, 1999), an independent outside radiologist found the child to have three measureable, enhancing brain lesions. The sum of the products of the greatest perpendicular diameters of these three lesions (SUM) was 16.49 cm². On April 12, 2000, after 5 months of ANP therapy, follow-up MRI revealed the sum to be 4.48 cm², a decrease of 72.8% from baseline while on June 23, 2003 a CR had been achieved (Figure 3).

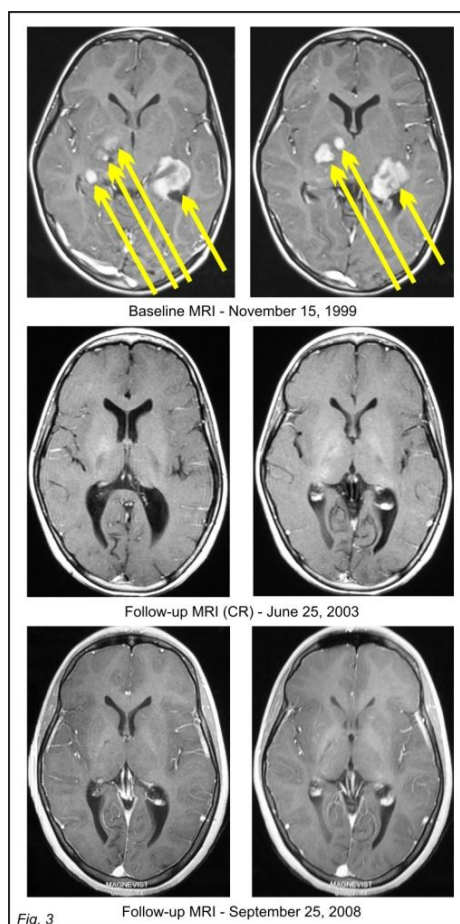


Figure 3. i) Baseline MRI (11/5/1999) showing a multicentric pilocytic astrocytoma in a 7-year-old female; ii) Follow-up MRI (6/25/2003) showing a complete response; and iii) Follow-up MRI (9/25/2008) showing persistence of the complete response.

The follow-up contrast-enhanced MRIs indicate the disappearance of multicentric nodules compared to the baseline MRI confirming complete response to ANP.

However, PET scan on April 5, 2000 had showed no tumor activity. Repeat PET scans on February 10, 2003, April 16, 2004 (just after permanent discontinuation of the oral formulations of A10 and AS2-1), and September 17, 2004 also showed no tumor activity, providing supporting evidence of the complete response seen on MRI. From March 10, 2000 to April 10, 2000, the child was off corticosteroids, but intermittently received small doses of corticosteroids after that. From June 23, 2000 to October 18, 2000 when corticosteroids were permanently discontinued, the patient received ≤ 1 mg of oral corticosteroids per day.

Over the course of her ANP therapy, the child experienced 6 Grade 1 and 2 ADEs that were possibly related to ANP therapy. All of these ADEs resolved with ANP therapy dose reduction or temporary discontinuation of ANP therapy.

The last documented follow-up with the patient's father was on July 21, 2015. At that time, the patient, age 22, had an OS since the start of ANP therapy of over 16 years. She was maintaining an excellent quality of life with no evidence of tumor recurrence. There has been no long-term disability related to ANP therapy. The patient has not received any additional anti-tumor therapy since ANP therapy was discontinued.

5. Discussion

In the context of CNS tumors, much remains unclear concerning the development of LDM. In addition, some controversy persists as to the differentiation of multifocal and multicentric disease, perhaps because the described pathophysiological basis for both is similar in some respects. In this report, disseminated disease refers to CSF dissemination, which can result in multicentric disease (Geer et al., 1997) and/or LM. Multicentric disease (and LM) can also occur because of the unique propensity of glioma cells to invade normal brain (or

spinal cord) and migrate long distances (Claes et al., 2007). The intent of this paper is to describe the efficacy of treating such disease with ANP therapy.

Overall survival with CNS AT/RT is poor with a median survival around 17 months (Athale et al., 2009). In phase II studies conducted at BC, 15 children with CNS AT/RT received ANP therapy, three of whom achieved an OR (20.0%). Table 2 presents a child with leptomeningeal and multicentric involvement who achieved a CR. There is no standard treatment for this rare tumor, but therapy for CNS AT/RT usually combines surgery, radiation therapy, and chemotherapy. More recently, high-dose chemotherapy with stem cell transplant has been advocated (Ginn et al., 2012). Due to the rarity of this tumor, it is not possible to define optimal therapy. There is insufficient peer-reviewed literature concerning CNS AT/RT to allow comparison of the efficacy of differing treatment regimens. However, based on our experience, ANP therapy should be considered in these cases.

Previously, we reported on ANP therapy in children with recurrent and progressive multicentric glioma (Burzynski, Weaver, Lewy, Janicki, Jurida, Bestak, 2004) and described favorable outcomes for children treated with ANP therapy when compared to children treated with radiation therapy and chemotherapy. We suggested that confirmation of these results through further studies could introduce a promising new treatment for incurable pediatric brain tumors.

As presented earlier, LDM have been associated with a poor prognosis in childhood brain tumors when compared to solitary lesions. However, we now report a 17.5% OR rate (i.e., 10 children) in 57 children with LDM following ANP therapy. Two- and five-year OS in the 57 children were both 28% while 10- and 15-year OS were both 26%. We are unable to find comparable series in the published literature but suggest that the data presented above indicate a definitive role for ANP therapy in the treatment of these children.

Most of the responding children are diagnosed with LGG.

Childhood LGGs are a heterogeneous set of tumors, encompassing astrocytic, oligodendroglial, and mixed glial-neuronal histologies (Sievert & Fisher, 2009). Although their clinical behavior can vary, the majority of LGGs are indolent and do not undergo malignant transformation. Case reports have even described spontaneous regression of some tumors (Rozen, Joseph & Lo, 2008; Parsa, Hoyt, Lesser, Weinstein, Strother, Hoyt, 2001). This is in contrast to adult LGGs that have a more aggressive phenotype. One reason for the differences between the two populations may be the different frequencies of histological subtypes. Pilocytic astrocytomas infrequently occur in adults but are the leading histology in children. Conversely, diffuse gemistocytic astrocytomas, which have been associated with an increased tendency toward malignant progression, are rarely found in children (Louis, 2007). LGGs are estimated to account for anywhere from 30% to 50% of CNS tumors in children (Freeman, Farmer & Montes, 1998; Blaney, Kun, Hunter, Rorke-Adams, Lau, ... Pollack, 2006; Pollack, 1999).

The two most common LGG histologies in children are the pilocytic (grade 1) and diffuse fibrillary astrocytoma (grade 2). The former occurs mainly in children aged 5 to 19 years with a peak incidence in the 5- to 9-year-old age range (CBTRUS, Supplement 4, 2015). Diffuse fibrillary astrocytomas occur in an older population with only 10% occurring below the age of 20 years (CBTRUS, Supplement 4, 2015). Pilocytic astrocytomas can arise anywhere in the central nervous system; however, they predominate in the cerebellum (Hayastek, Shaw, Scheithauer, O'Fallon, Weiland, ... Hu, 1993; Fernandez, Figarella-Branger, Girard, Bouvier-Labit, Gouvernet, ... Lena, 2003; Gajjar, Sanford & Heideman, 1997), optic pathway (Hoffman, Humphreys, Drake, Rutka, Becker, ... Greenberg, 1993; Sutton, Moloy, Sernyak, Goldwein, Phillips, ... Packer, 1995), and dorsally exophytic brainstem (Khatib, Heideman, Kovnar, Langston, Sanford, ... Greenwald, 1994). Conversely, diffuse fibrillary astrocytomas are more frequent in the supratentorial region, deep midline structures, and the cervicomedullary region (Louis, 2007; Weiner, Freed, Woo, Rezai, Kim & Epstein, 1997). Other, less common, LGG histologies in children include pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, subependymal giant cell astrocytoma, and oligodendroglioma.

LM has been reported to be uncommon in LGG with approximately 5% of LGG patients presenting with leptomeningeal dissemination at the time of diagnosis and 7% - 10% presenting with LM at the time of disease progression (Perilongo et al., 2003). The response criteria in LM differ between clinical studies, being based on a combination of radiologic (MRI), cytologic and clinical data. (Chamberlain et al., 2014). In this report we used radiologic OR and survival data.

It is difficult to discern the true incidence of multicentric gliomas from the single cases or small series reported in the published literature with estimates ranging from 2.5% to 9% (Courville, 1936; Batzdorf et al., 1962; Manzini et al., 1952; Russel et al., 1963; Willis, 1953; Zülch, 1957). However, the differentiation of multifocal and multicentric disease is problematic. In 1962, Batzdorf and colleagues (Batzdorf et al., 1962) thought that

multifocal gliomas disseminated along established CNS routes while multicentric gliomas were widely separated in location and/or time. By this definition, multifocal glioma consisted of tumors separated by white matter tracts within the same hemisphere, whereas multicentric glioma consisted of widespread tumors, such as those occurring in opposite hemispheres or separated by the tentorium. In contrast to this, Geer and Grossman, in 1997, suggested that interstitial fluid along white matter tracts could be a potentially important mechanism for the dissemination of glioma cells, explaining that glioma cells are inherently capable of migration along white matter tracts to distant areas of the brain (Geer et al., 1997). In 2007, Claes and colleagues (Claes et al., 2007) suggested that multicentric tumors are likely to develop because of the unique propensity of glioma cells to invade normal brain and migrate long distances.

6. Conclusions

We report our review of 57 children with LMD who were treated with ANP therapy in prospective phase II clinical trials utilizing ANP therapy. Of these children, ten (17.5%) had an objective response to therapy.

While the differentiation of multicentric and multifocal disease is problematic and awaits further definition, leptomeningeal disease is well defined. In our series, four of 21 children with leptomeningeal disease achieved an OR (19%), with two children (9.5%) achieving a PR, and two children (9.5%) achieving a CR. Based on these findings, we propose a single arm phase II clinical trial of patients with primary CNS tumors and leptomeningeal disease. In this single arm trial, the efficacy of ANP therapy in adult patients vs. children (< 18 years of age) would be compared. A randomized phase II clinical trial comparing ANP therapy to a regimen showing activity against leptomeningeal disease could also be considered.

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