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A Phase II Study of Antineoplastons A10 and AS2-1 in Children with Low-Grade Astrocytomas—Final Report (Protocol BT-13)

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Abstract

Nonresectable Low-Grade Astrocytomas (LGA) can compromise function and threaten life. For the majority of patients, the most appropriate strategy is initial chemotherapy followed by Radiation Therapy (RT). Since curative treatment is not available for most of these patients, it is reasonable to conduct clinical studies to evaluate new agents. This Phase II study evaluates efficacy and safety of Antineoplastons A10 and AS2-1 (ANP) in LGA. Sixteen children diagnosed with LGA were treated. They included 12 males and 4 females, ages 1.6 - 17.4 years (median 10.6). Efficacy was evaluated in 16 patients. The majority of patients were previously treated, but 1 patient had stereotactic biopsy only. Out of the remaining 15 patients, 6 patients received chemotherapy, and 7 patients had surgery, and 2 patients received RT and chemotherapy after surgery. The patients received treatment with ANP administered daily every 4 hours (median dose of A10 was 7.71 g/kg/d and AS2-1 was 0.26 g/kg/d) until objective response or stable disease was documented and for 8 months thereafter. The duration of ANP IV ranged from 1.4 to 286 weeks with a median of 83 weeks. A complete response was documented in 25.0%, partial response in 12.5%, and stable disease in 37.5%. Overall survival was 67.7% at 5 years, and 54.2% at 10 and 15 years. Progression-free survival was 48.1%, 34.4% and 34.4% at 5, 10, and 15 years respectively. The treatment was associated with grade 3 or grade 4 Adverse Drug Experiences (ADE) in 6 patients. There were two hypernatremias of grade 4 (12%). Grade 3 ADE included urinary frequency (6%), fatigue (6%) and hypernatremia (6%). There were no chronic toxicities, and there was a high quality of survival. ANP shows efficacy with a very good toxicity profile in this cohort of children with low-grade astrocytoma.

Keywords

Antineoplastons A10 and AS2-1, Astrocytoma, Low-Grade Astrocytoma,

Low-Grade Glioma, Pediatric Brain Tumors, Phase II Clinical Trial

1. Introduction

Low-Grade Astrocytomas (LGA) are the most common type of pediatric glioma, and they account for over 1000 new cases in the United States in 2015 [1]. LGA grade 1 (Pilocytic Astrocytoma (PA)) has a relatively favorable prognosis, particularly if complete excision is possible, but the pilomyxoid variant of PA can be more aggressive and more likely to disseminate [2]. Although metastases are unlikely, tumors can be of multicentric origin. Children with neurofibromatosis type 1 (NF-1) constitute a special subset of patients with LGA. In general, therapy is not performed for incidental tumors found with surveillance scans, but symptomatic tumors and those that progress require treatment. The treatment for low-grade supratentorial astrocytoma is determined by location. Radiation Therapy (RT) is often reserved until disease is progressive [3]. Due to the debilitating effects of RT on growth and neurological development, chemotherapy is commonly employed in young children to delay RT [4] [5]. A number of chemotherapy regimens have been tested, including carboplatin and vincristine as well as, nitrosourea-based multiagent regimens including procarbazine, 6-thioguanine, dibromodulcitol, lomustine and vincristine, and single agent temozolomide [4] [5] [6] [7].

Unfortunately, based on the most recent studies, the traditional regimen with carboplatin and vincristine introduced 19 years ago still provides the best results [7]. There is no doubt that chemotherapy has been successful in stabilizing disease and delaying inevitable radiation therapy and death from tumor progression. Conquering the disease by complete elimination of the tumor and providing the patient with high quality of life and normal life expectancy seems to be still far away, and chronic toxicity continues to be a major obstacle [8].

Antineoplastons A10 and AS2-1 (ANP) are synthetic derivatives of glutamine, isoglutamine and phenylacetic acid [9]. A10 is a synthetic formulation consisting of a 4:1 ratio of phenylacetylglutaminate sodium (PG) and phenylacetylisoglutaminate sodium (isoPG). AS2-1 is a synthetic formulation with a 4:1 ratio of phenylacetate sodium (PN) and PG. In the Phase II study of ANP in 20 patients with astrocytomas conducted in 1988, a Complete Response (CR) and over 28 years Progression-Free Survival (PFS) was documented in the treatment of a 7-year-old child diagnosed with a large pilocytic astrocytoma [10] [11]. This patient did not have surgery, RT or chemotherapy. Additional clinical studies of ANP documented numerous objective responses and cases of long-term survival in pediatric and adult high-grade glioma, brainstem glioma, including Diffuse Intrinsic Pontine Glioma (DIPG), and medulloblastoma [12]-[24]. Based on positive preliminary results, we decided to design and conduct a single arm Phase II study of ANP to assess the efficacy and safety in children diagnosed with LGA.

2. Patients and Method

2.1. Study Design

Patients, over 6-months-old, with evidence of unresectable LGA by gadolinium-enhanced Magnetic Resonance Imaging (MRI) performed within two weeks prior to study enrollment, were recruited into this study if the diagnosis was confirmed by an outside pathologist.

Eligibility criteria included a Karnofsky Performance Status (KPS) of 60 - 100, but additional patients with KPS below 50 could be accepted based on case-by-case evaluation and with exception granted by the Food and Drug Administration (FDA). The protocol allows self-administration of ANP which requires a KPS of over 50. Additional eligibility criteria have previously been described [12]. Patients whose primary tumors were located in the brainstem were excluded. Additional exclusion criteria have previously been described [12]. The use of corticosteroids was permitted to reduce symptoms and signs attributed to cerebral edema, but it was recommended that the smallest doses compatible with the preservation of optimal neurologic function, be used.

All study subjects and/or guardians read, understood, and signed a written informed consent document prior to enrollment. This study was conducted in accordance with the U.S 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 Industry. The study was sponsored by the Burzynski Research Institute, Inc. (BRI) and conducted by the Burzynski Clinic (BC) in Houston, Texas. It was performed according to Protocol BT-13, which was submitted to the FDA under the IND 43,742. It was supervised by an independent Institutional Review Board (BRI-IRB). The study commenced on May 2, 1996 and continued through June 13, 2007. Patients were removed from the study before completion of treatment for reasons that have previously been described [12].

The protocol was amended occasionally by BRI; however, the amendments did not alter the aim or design of the original study objectives/outcomes and did not affect patient safety.

2.2. Statistical Considerations

The study was designed as a single-arm, two-stage, interventional Phase II trial of ANP as the monotherapy in a high-risk, poor-prognosis study population [25]. Calculation of sample size and study endpoints have been previously described [12]. The minimum sample required for this study to prove efficacy was based on a minimum number of 4 participants with Objective Response (OR).

Survival and time to treatment failure was measured from the first day of ANP administration until 1) death from any cause and 2) the date of first observation of progressive disease or death from any cause (whichever came first), respectively. The distributions of survival and treatment failure were estimated by Kaplan-Meier analysis.

2.3. Treatment Plan

ANP A10 and AS2-1 were delivered via a dual-channel infusion pump and single-lumen subclavian catheter (Broviac or Groshong) every 4 hours. On the first day of administration of ANP, the flow rate of the pump was maintained at 25 mL/h. Beginning from the second day, individual injections were given at 50 to 250 mL/h depending on the patient's age and tolerance [12] [13].

On the first day of treatment, the pump was loaded with 60 mL of ANP A10 (0.3 g/mL) and 60 mL of ANP AS2-1 (0.08 g/mL). The volume of each injection was 10 mL administered every 4 hours, 6-times a day. Beginning from the second day of treatment in children younger than 12 years of age, the dose of each injection was increased on a daily basis in increments of 10 mL until the highest tolerable dose or effective dose was reached, not exceeding 25 g/kg/d of ANP A10 and 0.3 to 0.6 g/kg/d for ANP AS2-1. For children 12 years of age or older the dose of ANP A10 was escalated in increments of 20 mL, and over 16 years of age in increments of 40 mL. When the study subject reached an effective dose, or the highest tolerated dose, the "escalation phase" of the treatment stopped. The effective dose was defined as the universal dosage, which in previous studies was associated with OR. The subject continued the daily administration of six doses of A10 and AS2-1 (every four hours via automated pump) until a response to the treatment was determined. The subject was then advised to continue treatment for at least eight months after a treatment response was documented. ANP treatment was stopped at the patient's request or if their clinical condition worsened.

The rationale for using two formulations of antineoplastons was based on prior clinical trials, pharmacokinetic studies and laboratory research [9] [10]. The escalation of the dosage of ANP was required based on the results of prior studies carried out to determine whether patients were able to tolerate large volume infusions of intravenous fluids associated with higher doses of ANP [9]. As a safety precaution it is recommended that the escalation of the dosages will continue through Phase II and Phase III trials programs.

Medications that were considered necessary for the subjects' welfare and that did not interfere with the evaluation of treatment were given at the discretion of the investigator. The use of corticosteroids was carefully monitored. Treatment with other antineoplastic or immunomodulatory agents was not permitted during the study. Subjects received full supportive care, including transfusions of blood products and antibiotics when appropriate. No other anticancer medication was permitted.

The initial three weeks of therapy were administered by BC staff on an outpatient basis, in Houston, Texas. The treatment did not require hospitalization. Subjects and/or their legal guardians were trained by clinic staff to self-administer antineoplaston therapy during this time. Starting on week 4, ANP therapy was administered at home with 24-hour support available via phone or email. Treatment and monitoring of the subject's condition, once released to self-administered therapy, continued under the supervision of the subject's local physician.

2.4. Evaluation and Follow-Up

Prior to the start of treatment, a gadolinium-enhanced MRI measured all contrast-enhancing lesions.

One patient did not have contrast-enhanced lesions, and additional two patients could not be given contrast medium. In these patients the measurements were preformed on T1 weighted images.

The products of the two greatest perpendicular diameters of all lesions were calculated and totaled, providing a baseline evaluation for each study subject. As a common practice at that time in other clinical trials, the tumor measurements were based on contrast enhanced lesions, but the overall tumor size was also measured including T2 and FLAIR images [26].

The baseline provided the reference for determining response outcomes to the treatment. Blood and urine tests (complete blood count with differential, platelet count, reticulocyte count, and serum chemistry) anticonvulsant serum levels, prothrombin time, and partial thromboplastin time were carried out on all subjects prior to the start of treatment to establish normal baselines. The additional pretreatment measurements included KPS, vital signs, clinical disease status, demographics, medical history and current medications, physical examination with neurologic emphasis, chest x-rays and electrocardiogram (EKG).

In accordance with other Phase II studies conducted at the initiation of this trial, the possible responses to the treatment were CR, PR, SD and Progressive Disease (PD). CR required the disappearance of all enhancing lesions, sustained for at least 4 weeks, and only physiologic replacement doses of steroids were acceptable. PR required 50% or higher decrease of the sum of the products of the two largest perpendicular diameters of enhancing lesions and stable or reduced corticosteroid doses. PD was determined when there was over 50% increase of enhancing lesions or new lesions, and SD was the status between PR and PD.

The results of all MRI and PET scans were verified by radiologists not affiliated with BRI or BC and their determination of response was accepted.

Study subjects were categorized by their overall best response during the course of the treatment. The duration of each response was measured from the date that the criteria for the outcome were first met until the date that PD was first documented. In the case of SD, the duration was measured from the time therapy commenced.

The number of patients was in the range of the other studies for recurrent LGG conducted at the same time and is comparable to similar studies conducted in this patient population. The slow accrual rate of patients to this study resulted in a longer than expected study duration. In addition the decision was taken by the investigator to extend the study evaluation/observation period time once 4 patients achieved a CR/PR etc.

Toxicity was evaluated in all patients (16 patients had an LGA while one patient had a grade 3 astrocytoma).

Data on Adverse Drug Experiences (ADEs) were collected during the initial 3 weeks of ANP therapy by clinic staff at the BC.

When study subjects transitioned to home-based therapy administration, clinic staff made daily telephone contact for the first two months to ensure protocol compliance, to resolve any issues with therapy administration, and to continue assessing ADEs. Weekly contact was made starting in third month.

MRIs were repeated at least every 8 weeks during the first 2 years unless the patient's condition or confirmation of response required MRI within 4 weeks.

Positron Emission Tomography (PET) scans were performed as necessary.

Continued patient treatment with ANP was determined on a weekly basis and based upon the trial protocol, patient health status, and the response to treatment. The ADEs were graded according to Version 3 of the Common Terminology Criteria for Adverse Events (CTCAE v.3). Pharmacokinetic studies have been carried out in earlier Phase I and other Phase II studies and were not included in the study. Based on prior study there was no indication of interference with some medications, in particular, anti-seizure drugs.

3. Results

3.1. Patient Demographics

Subject enrollment started May 2, 1996, and continued through June 13, 2007. As of January 20, 2009, all subjects were removed from the therapy due to a CR, subject request, PD, or worsening clinical condition. The 16 candidates who met eligibility criteria had a median age of 10.6 years. There was distribution between genders (25% female, 75% male), and the majority of subjects (81.25%) were Caucasian. 10 patients underwent partial tumor resection; 5 patients had craniotomy and excisional biopsy; 2 patients underwent radiation; 8 patients were treated with chemotherapy.

Demographics for the subjects are summarized in Table 1.

Patient demographics did not change during the study, and were similar to the other studies on pediatric Low-Grade Gliomas (LGG). The trial enrolled 11 LGA study subjects and 5 LGA patients received ANP under Special Exception.

3.2. Treatment

The maximum daily dose of antineoplaston A10 ranged from 4.04 to 24.11 g/kg/d with a median of 11.52 g/kg/d. For AS2-1, the median daily dose was 0.38 g/kg/d, with a range of 0.23 to 1.56 g/kg/d. The average maximum effective daily dose of A10 in subjects with an OR (calculated to the first MRI of PR or CR) was 11.35 g/kg/d (range 6.89 to 20.30 g/kg/d). The duration of IV ANP therapy ranged from 1.4 to 286 weeks with a median of 83 weeks. Six subjects had an OR and therapy ended after a median of 114 weeks of intravenous treatment.

3.3. Response and Survival

Out of 16 enrollees, four (25%) had CR, and two had PR (12.5%), 6 (37.5%) had SD, 1 (6.3%) had PD (Figure 1 and Figure 2). Three patients did not have PD and were too short on treatment to be evaluated as SD. It took a median of 136 days for the beginning

Table 1. Study demographics-Protocol BT-13, Low-Grade Astrocytomas.

Characteristics	Demographics
Median age (years)	10.6
Range of ages (years)	1.6 - 17.4
Male	12
Female	4
Ethnicity	W-13, I-1, M-1, Y-1
Tumor Type	
Astrocytoma	5
Astrocytoma fibrillary	2
Astrocytoma pilocytic	9
Karnofsky Performance Score	
Median	70
40	1
50	3
60	3
70	2
80	3
90	3
100	1
Prior Treatment	
Stereotactic biopsy	1
Excisional biopsy	3
Excisional biopsy and Chemotherapy	2
Partial resection	4
Partial resection and chemotherapy	4
Partial resection, chemotherapy and radiation therapy	2

Note. BSG—brainstem glioma, W—Caucasian, M—Hispanic, I—Indian, Y—Oriental.

of the OR to be reached (range 92 to 883 days).

CR was determined in 4 cases. PR was determined in 2 cases.

Table 2 shows response to antineoplaston treatment compared to Phase II studies with chemotherapy for low-grade astrocytoma.

Seven patients diagnosed with LGA are currently alive over 17 years since the treatment start after response was classified as OR.

Post-treatment KPS increased in 8 patients (50%), was stable in 8 patients (50%).

During the study the generally accepted criteria for evaluation of responses changed toward reliance on overall survival (OS) and PFS rather than tumor responses. As a re-

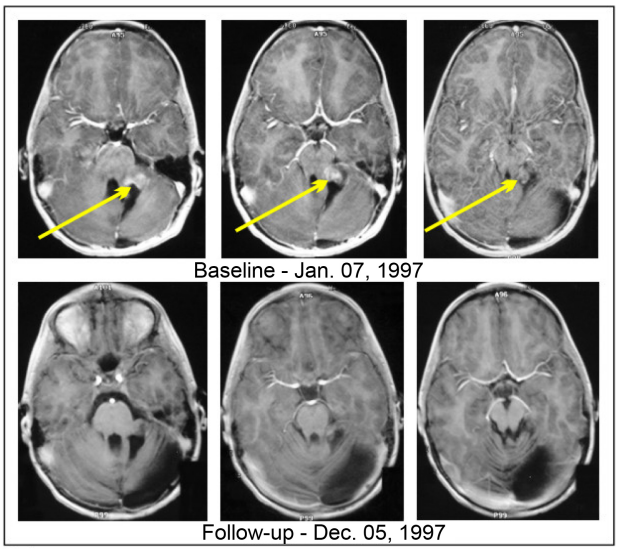

Figure 1. Pilocytic astrocytoma of the cerebellum in a 6-year-old male treated in the study from January 14, 1997 to October 15, 1998. Recurrence after gross total resection of the tumor on August 12, 1996 without radiation therapy or chemotherapy. MRI of the head, T1 post-contrast. Baseline versus follow-up showing complete response. Overall survival from treatment start is over 19 years. The yellow arrows indicate contrast-enhancing lesions.

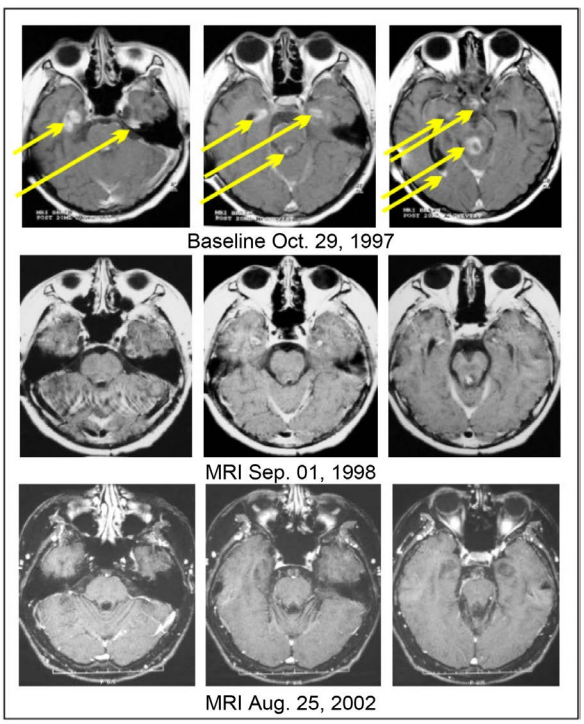

Figure 2. Pilocytic astrocytoma, disseminated to the brain and spinal cord in a 16-year-old male, post-excisional biopsy of the tumor, but without radiation therapy and chemotherapy. Treated with intravenous antineoplastons A10 and AS2-1 under Special Exception from November 5, 1987 until April 7, 2003. MRI of the head, T1-post-contrast. Baseline versus follow-ups showing complete response. Overall Survival from treatment start was over 18 years. The yellow arrows indicate contrast-enhancing lesions.

Table 2. Response to antineoplaston treatment compared to Phase II studies with chemotherapy for low-grade astrocytoma.

Author/ Treatment	Patient No.	Efficacy Response (%)			PFS (%)				Survival (%)					
		CR	PR	SD	2 years	3 years	4 years	5 years	2 years	3 years	4 years	5 years	10 years	15 years
Packer, *et al.* 1997 [4] Carboplatin, Vincristine	78	5.1	28.2	60.2	75	68	-	-	-	-	-	-	-	-
Prados, *et al.* 1997 [5] Nitrosourea and multiagent chemotherapy	42	0	35.7	59.5	-	45	-	-	-	-	-	78	-	-
Gururangan, *et al.* 2002 [6] Carboplatin	80	2	17	50	-	64	-	-	84	-	-	-	-	-
Burzynski, *et al.* 2016, Antineoplastons	16	25	12.5	37.5	61.9	55.0	48.1	48.1	81.3	74.5	67.7	67.7	54.2	54.2

Note. CR—complete response, OS—Overall survival, PFS—progression-free survival, PR—partial response, SD—stable disease.

sult this paper also includes survival data.

Survival analysis revealed a median PFS of 37.1 months and PFS at six months of 68.8%. The survival at 2 and 5 years is 81.3% and 67.7%, and remains 54.2% in excess of 15 years. Eight patients are alive and well over 10 years since treatment start. The Kaplan-Meier survival curve is shown in **Figure 3**.

3.4. Adverse Events

Safety assessments were analyzed based upon the total number of enrolled patients in the study. Intense monitoring of patient safety was conducted during the first two months of therapy and involved daily direct questioning concerning adverse events, first at the clinic and then followed by daily phone calls during the home administration phase. After two months, telephone contact was conducted on a weekly basis. Adverse events were categorized according to the CTCAE v.3, and compared to other studies (see **Table 3**). A detailed report on ADEs can be found on the Child's Nervous System website. No long-term ADEs to ANP were reported. Brain tumor patients frequently receive corticosteroids as part of their therapeutic regimen to reduce cerebral edema around tumors. The use of corticosteroids, the infusion of large volumes of sodium-containing solutions during antineoplastons therapy, and the brain tumor itself predispose a patient to an increased incidence of serum sodium concentration abnormalities. As a result, Grade 3 and Grade 4 reversible hypernatremia was reported in 2 cases.

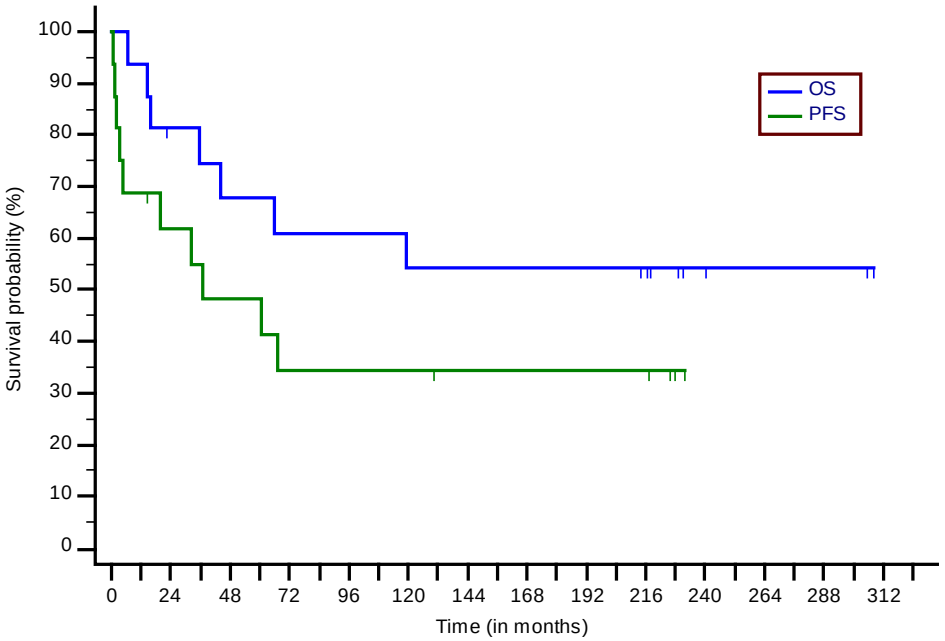

Figure 3. The Kaplan-Meier survival curve. *Note*: OS-overall survival from treatment start, PFS-progression-free survival from treatment start.

Table 3. Incidence of adverse drug experiences, Grades 3, 4 or 5 reported by patients during antineoplaston treatment compared to other studies of chemotherapy for low-grade astrocytomas.

Adverse Drug Event	Burzynski, *et al.* 2016, Antineoplastons		Packer, *et al.* 1997 [4] Carboplatin, Vincristine		Prados, *et al.* 1997 [5] Nitrosourea and multiagent chemotherapy		Gururangan, *et al.* 2002 [6] Carboplatin
	Grade 3/(%)	Grade 4/(%)	Grade 3 and 4	Grade 5/(%)	Grade 3/(%)	Grade 4/(%)	Grade 3 and 4 (%)
Hypokalemia	1 (6%)	1 (6%)					
Hypernatremia	1 (6%)	2 (12%)					
Somnolence	1 (6%)						
Thrombocytopenia			*			3 (7%)	40 (49%)
Neutropenia						2 (5%)	55 (68%)
Infection							12 (15%)
Allergic reaction			*				4 (5%)
Neuropathy			*				
Nausea					1 (2%)		
Septicemia				1 (1%)			

Note. *—No data were provided except that 5 patients were removed from the study because of allergic reaction, and occasional delays in treatment were caused by prolonged thrombocytopenia and neurotoxicity.

4. Discussion

The treatment of LGG in children continues to create controversy. The response to

therapy, the unpredictable outcome and spontaneous behavior in some patients are the most important factors which interfere with defining the standards of care. The advancement in surgery, RT and chemotherapy is not yet translated into curative treatment for most of the patients [27]. Clinical studies on LGG have been reviewed in the literature [8]. Despite considerable progress in basic research, the most attractive treatment is still older than the 15-year regimen of carboplatin and vincristine [4]. Large studies revealed 86% and 88% OS at 5 years by using such regimen and continuation of impressive OS rate until 10 years [7]. It is realized that LGA comprises a heterogeneous group of brain tumors with over 800 genomic and numerous epigenomic abnormalities [28] [29] [30] [31]. In the era of personalized treatment, it is clear that effective and possibly curative treatment requires the agents which target specific genes involved in subgroups of patients [18]. Such treatment may provide lower median OS and PFS rates, but can give long-term tumor free survival for a subgroup of patients with specific genomic abnormalities.

The results of this study are tabulated and compared to the other clinical trials with a small population of children with LGA (**Table 2**).

ANP shows a remarkably higher CR rate, which is 25%, compared to 0% to 5% in the other studies.

PR rate is substantially lower (12.5% versus 12% to 36%).

Overall survival up to five years is lower than in the other studies, but it persists over 10 and 15 years at 54.2%.

These patients live normal and high quality lives, and are tumor-free. This seems to be characteristic of ANP treatment.

Since this therapy works on multiple genetic targets, it is understandable that it can provide very good responses and long-term survival in the susceptible subpopulation of patients [9]. The toxicity profile of ANP is excellent compared to the other studies, with only a small percentage of easily reversible Grade 3 - 4 toxicities and no chronic toxicities (**Table 3**) [4]-[6].

Currently, our group attempts to identify genomic abnormalities in our patient population and correlate them with response to ANP.

This small Phase II study of ANP in pediatric LGA demonstrated a high CR rate of 25%, and a total disease stabilization rate of 75% (CR/PR/SD). It offers over 50% overall survival over 15 years. The safety of the treatment is remarkable, with no chronic toxicities and a small percentage of easily reversible Grade 3 - 4 ADEs. It is recognized that the study is limited by a population without a control cohort. However, the patient population in the study is representative of the general population at risk, and the efficacy and safety were properly evaluated. The additional limitations of the study include the use of the pump, mobility in the outpatient regimen, the need of training and the extreme amount of hygiene related to the use of the intravenous catheter. It is the author's opinion that this study provides evidence supporting the safety and efficacy of ANP in the treatment of LGA, which should be confirmed by further research including Phase 3 studies.

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