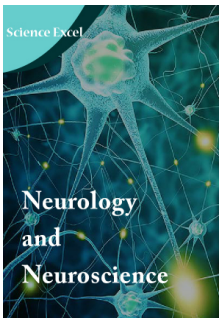
Neurology & Neuroscience

Original Article



Newly Diagnosed Anaplastic Astrocytoma: > 23 Year Survival in a 31-Year and 11-Month-Old Female Treated with Antineoplastons

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- Received Date: 19 Apr 2023
- Accepted Date: 10 May 2023
- Publication Date: 08 Jun 2023

Keywords

Antineoplastons; Brain tumor; Anaplastic astrocytoma, Newly diagnosed anaplastic astrocytoma, Phase II study.

Abstract

Rationale: Anaplastic astrocytoma (AA), a malignant brain tumor that arises from astrocytic cells, has a poor prognosis. It accounts for 6–7% of gliomas and 1-2% of brain tumors. **Objectives:** A 31-year and 11-month-old female with an AA is presented to discuss the efficacy of Antineoplastons A10 (Atengenal) and AS2-1 (Astugenal) in the treatment of AA. She presented to the Burzynski Clinic (BC) for treatment and was enrolled in Protocol BT-08, "Phase II Study of Antineoplastons A10 and AS2-1 in Adult Patients with Anaplastic Astrocytoma", receiving both intravenous (IV) and oral Antineoplastons A10 and AS2-1 (ANP therapy). IV ANP therapy was delivered continuously via subclavian catheter and infusion pump. Tumor response was determined by comparison of baseline brain magnetic resonance imaging (MRI) to sequential brain MRIs during therapy. **Findings:** The patient presented to the BC with no prior treatment and a one-month history of right arm clumsiness and right leg weakness. Brain MRI and stereotactic biopsy performed elsewhere had demonstrated an AA. Baseline MRI at the BC showed a 2.0 cm^2 non-enhancing lesion and two enhancing lesions (0.02 cm^2 and 0.15 cm^2) in the left parietal lobe. IV ANP therapy was given over 56 days, and a complete response (CR) was demonstrated after one month of therapy. Oral ANP therapy was subsequently provided for 17 months. At last follow-up, in June 2023, the patient was healthy and showed no evidence of recurrent disease. She had an overall survival (OS) of > 23 years and one month since diagnosis and an OS of > 23 years since the start of IV ANP therapy. **Conclusions:** The utilization of ANP therapy in an adult female patient with AA is presented. The patient achieved a CR and prolonged OS, suggesting that ANP therapy may be an effective therapeutic option for adults with AA. .

Introduction

Anaplastic astrocytoma (AA) is a primary malignant brain tumor, which arises from astrocytic cells. It accounts for 6–7% of all gliomas and nearly 1-2% of all brain tumors. The median age of presentation is 41 years. According to the 2007 World Health Organization (WHO) classification, AA is grade III or IV [1].

The WHO 2016 classification considered molecular characteristics in addition to the morphological aspects of the tumor [2]. AA has both isocitrate dehydrogenase (IDH) wild-type and IDH-mutant variants and, unlike anaplastic oligodendroglioma, is 1p/19q non-co-deleted (see Discussion). IDH wild-type gliomas usually have a more aggressive behavior although the morphological characteristics of the two variants are similar. Other molecular alterations (EGFR and/or TERT promoter amplification) are frequently present in IDH wild-type AA [3,4].

Morphological features of AA include increased cellularity, MIB-1 labeling index of 5–10%, increased mitoses, nuclear pleomorphism and atypia, the presence of glial markers, and the absence of neuronal markers [5]. Necrosis and vascular proliferation are not prominent [6]. Magnetic resonance imaging (MRI), with gadolinium contrast, remains the gold standard for diagnosis and for monitoring response to treatment. AA usually appears as a T1-weighted hypointense and T2-weighed hyperintense mass with enhancing nodular areas, although one-third of AAs do not show enhancement [7]. AA has a homogeneous signal intensity in T2-weighted sequences, has a well-defined margin, and only occasionally invades the cerebral cortex [8]. Positron emission tomography (PET) scan can be helpful in determining AA response to treatment.

The clinical presentation of AA is variable and includes neurological deficits, headaches, visual and sensory impairment, speech disorders, loss of strength, and gait

Citation: Burzynski S, Burzynski G, Janicki T, Beenken S. Newly diagnosed Anaplastic Astrocytoma: > 23 Year Survival in a 31-Year and 11-Month-Old Female Treated with Antineoplastons. Neurol Neurosci. 2023;4(2):1-6.

disturbances.

Maximum surgical resection remains the primary therapy of AA [9]. A second surgery can be considered following incomplete resection or in the case of recurrent disease. Radiation therapy (RT) and chemotherapy are utilized for AA following surgical therapy. Molecular characteristics, age, performance status, type of surgery, size and location of the tumor are considered prognostic factors [10].

We present here the successful use of ANP therapy (Antineoplaston A10 {Atengenal} and Antineoplaston AS2-1 {Astugenal}) in the treatment of an adult female with a newly diagnosed AA.

Materials and methods

In May 2000, a 31-year and 11-month-old female developed right upper extremity clumsiness and weakness of the right leg. She sought medical attention from her chiropractor, who referred her to a neurologist. An MRI of the brain, performed on May 10, 2000, revealed a 2.0 cm^2 mass in the left parietal lobe. Computerized tomography (CT) scans of the chest, abdomen and pelvis were performed on May 11, 2000, and were found to be normal. On May 15, 2000, the patient underwent stereotactic biopsy of the left parietal tumor. Histological examination of the microscopic slides revealing an AA.

The patient elected to be evaluated and treated at the Burzynski Clinic (BC). She had not had a surgical resection, RT, or chemotherapy. Baseline MRI of the brain, with gadolinium contrast, performed on June 1, 2000, showed a 2.0 cm^2 non-enhancing lesion and two enhancing lesions (0.02 cm^2 and 0.15 cm^2) in the left parietal lobe (Figure 1). On June 6, 2000, the patient began intravenous (IV) ANP therapy according to Protocol BT-08, "Phase II Study of Antineoplastons A10 and AS2-1 in Adult Patients with Anaplastic Astrocytoma". In this single arm study, IV ANP therapy was delivered every four hours via a subclavian catheter and a programmable infusion pump.

The objectives of BT-08 were to 1) determine the efficacy of ANP therapy in adults with AA; 2) determine the safety and tolerance of ANP therapy in this group of patients; and 3) determine objective response (OR) utilizing brain MRI scans, which were performed every 8 weeks for the first two years, and then less frequently.

Eligibility criteria for BT-08 included 1) histologically confirmed AA; 2) evidence of AA as determined by brain MRI performed within seven days of the initiation of treatment; 3) age of ≥ 18 years; 4) Karnofsky Performance Status (KPS) ≥ 60%; and 5) life expectancy ≥ 4 months.

Gadolinium enhanced MRI of the brain was used in the diagnosis, response to treatment, and follow-up of AA. T2-weighted, T2-fluid attenuated inversion recovery (T2-FLAIR), T1 weighted, and T1-weighted contrast-enhanced images were obtained. AAs are usually gadolinium-enhancing, therefore sequential T1-weighted contrast-enhanced images were utilized to determine the effect of therapy [11].

As determined by MRI of the brain, the product of the two greatest perpendicular diameters of each measurable and enhancing lesion was calculated. Tumor size was defined as the sum of these products [12]. The response criteria were as follows: a complete response (CR) indicated complete disappearance of all enhancing tumor while a partial response (PR) indicated a 50% or greater reduction in total measurable and enhancing tumor size. CR and PR required a confirmatory brain MRI performed at least four weeks after the initial finding. Progressive disease (PD) indicated a 25% or greater increase in total measurable and enhancing tumor size, or new measurable and enhancing disease, while stable disease (SD) did not meet the criteria for PR or PD [12].

Protocol BT-08 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 (ICH) and Guidance for Industry (FDA). By participating in this study protocol, the investigators agreed to provide access to all appropriate documents for monitoring, auditing, IRB review and review by any authorized regulatory agency.

Results

The adult female presented here was evaluated and treated at the BC following stereotactic biopsy of a left parietal tumor, which provided the diagnosis of AA. At last follow-up in June 2023, she was doing well, had no evidence of tumor recurrence, had an overall survival (OS) of > 23 years and one month since diagnosis, and an OS of > 23 years since the start of IV ANP therapy.

The starting dose of IV A10 for this patient was 1.41.g/kg/d while the starting dose of IV AS2-1 was 0.25 g/kg/d. The doses of intravenous (IV) A10 and AS2-1 were gradually increased to 12.47 g/kg/day and 0.40 g/kg/day, respectively. A10 was subsequently reduced to 6.05 g/kg/day while AS2-1 was subsequently reduced to 0.30 g/kg/day. Throughout her IV ANP therapy, the patient experienced elevations in SGOT and SGPT, which interrupted and limited her therapy. MRI of the brain on July 3, 2000, one month after initiation of ANP therapy, demonstrated complete resolution of the enhancing disease in the left parietal lobe, indicating the achievement of a CR (Figure 1). The 2.0 cm^2 non-enhancing tumor remained. MRI of the brain on July 31, 2000, again demonstrated complete resolution of the enhancing disease confirming the CR. On August 1, 2000, IV ANP therapy was terminated. Oral ANP therapy began on August 5, 2000.

The starting dose of both oral A10 and AS2-1 for this patient was 0.01 g/kg/d. The doses of A10 and AS2-1 were gradually increased to 0.30 g/kg/d and 0.29 g/kg/d, respectively. Both were subsequently reduced to 0.18 g/kg/day. The patient continued these doses of oral ANP therapy until June 3, 2002, when she elected to end therapy. The oral ANP therapy doses were then gradually reduced, and the patient discontinued all ANP therapy on November 1, 2001. Long-term, follow-up brain MRI, on February 6, 2017, showed complete disappearance of the 2.0 cm^2 non-enhancing nodule and the two enhancing nodules in the left parietal lobe indicating an enduring CR and complete disappearance of all tumors (Figure 1).

All MRIs of the brain showing an OR were reviewed by a prominent outside neuroradiologist. Consent was obtained from the patient for publication of the brain MRI images (Figure 1) and the post-treatment photograph (Figure 2) presented in this report.

Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE v.3). The patient presented here experienced two serious adverse events (SAEs), both of which resolved completely.

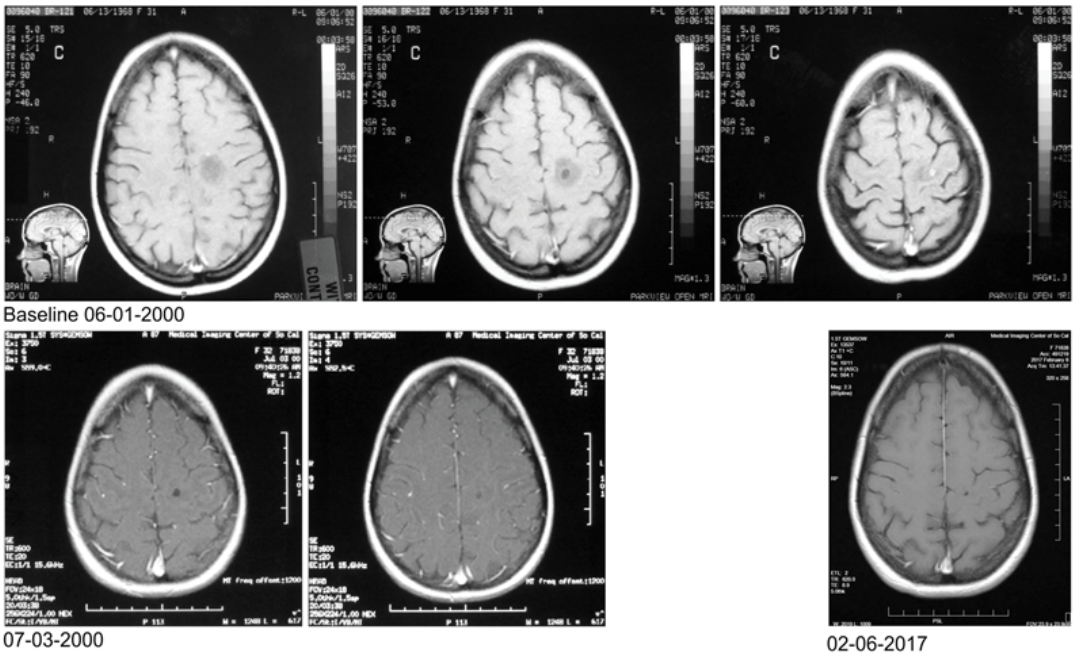

Figure 1. ***Axial MRI Images: 06-01-2000:*** *this baseline set of images, in each instance, shows a 2.0 cm² non-enhancing nodule in the left parietal lobe while the left-sided image shows a 0.15 cm² enhancing nodule situated anteriorly and the right-sided image shows a 0.20 cm² enhancing nodule situated medio-laterally;* ***07-03-2000****: there is disappearance of the enhancing nodules in the left parietal lobe, indicating a CR, while the non-enhancing nodule persists;* ***02-06-2017:*** *there is complete disappearance of the 2.0 cm² non-enhancing nodule in the left parietal lobe and the two enhancing nodules indicating an enduring CR and complete disappearance of all tumor. CR=Complete response; MRI=magnetic resonance imaging.*

Figure 2. *Photograph of post-treatment patient.*

Discussion

Primary therapy for AA continues to be maximal surgical resection [9]. Biopsy of the tumor can be performed if maximal resection is not possible. Trials comparing biopsy vs. resection have been uncontrolled and have contained considerable selection bias. Despite these limitations, these trials demonstrated better survival in patients who underwent maximal surgical resection. [10].

Surgery alone is not curative for AA and adjuvant treatment is always considered. Post-operative RT is frequently employed. It is administered to the gadolinium-enhancing areas and to the hyperintense T-2 weighted / FLAIR areas, while adding a 1.5–2.5 cm margin to this treatment area [9]. The total RT dosage is 59.4 Gray (Gy), with fractions of 1.8 Gy, 5 days per week.

Post-surgical chemotherapy has been compared with RT as an initial treatment of anaplastic gliomas in several randomized studies. A prospective randomized phase III study, the NOA-04 trial, randomized anaplastic glioma patients to initial treatment with 1) RT or 2) chemotherapy with a PCV regimen (procarbazine, lomustine and vincristine) or temozolomide (TMZ) [13]. In this study, chemotherapy with deferred RT showed no advantage over RT alone. However, long-term analysis demonstrated the importance of IDH mutational status on progression-free survival (PFS)[14]. Methylation of the promoter of the O6-methylguanine-DNA transferase (MGMT) promoter was associated with improved PFS in chemotherapy arms, but only in patients with wild-type IDH. Since TMZ is less toxic than the PVC regime, it is considered the drug of choice in this group of patients.

Subsequently, M. van den Bent, and colleagues presented data from a phase III, randomized open-label study, suggesting that adjuvant TMZ appeared to increase OS in anaplastic glioma patients [14,15]. Eligible patients were ≥ 18 years of age, had newly diagnosed 1p/19q non-co-deleted anaplastic glioma, and a WHO performance status score of 0-2. Between December 2007 and September 2015, 751 anaplastic glioma patients were randomly assigned to 1) RT alone (n=189); 2) RT with concurrent TMZ (n=188); 3) RT with adjuvant TMZ (n=186); and 4) RT with concurrent and adjuvant TMZ (n=188). Patients were stratified by institution, WHO performance status score, age, 1p loss of heterozygosity, the presence of oligodendroglial elements on microscopy, and MGMT promoter methylation status. While concurrent TMZ was not shown to affect OS, adjuvant TMZ increased OS (82.3 months) when compared with no adjuvant TMZ (OS=46.9 months) ($p<0.0001$). The authors concluded that adjuvant TMZ, but not concurrent TMZ chemotherapy was associated with a survival benefit in patients with 1p/19q non-co-deleted anaplastic glioma.

Single agent targeted therapy for AA is now being investigated. To date, no survival benefit has been demonstrated. A comprehensive overview of targeted therapy in AA has been presented by M. Caccese and colleagues [16]

ANP research began in 1967, when significant deficiencies were noticed in the peptide content of the serum of patients with cancer compared with healthy persons. Initially ANP were isolated from the blood and later from urine [17]. Subsequent studies of the isolated ANP demonstrated that Antineoplaston A-10 and Antineoplaston AS2-1 were the most active ANPs. The chemical name of Antineoplaston A-10 is 3-phenylacetylamino-2,6-piperidinedione. It consists of the cyclic form of L-glutamine connected by a peptide bond to phenylacetyl residue. Its active components are phenylacetylglutamine (PG) and phenylacetylisoglutaminate (isoPG). When given orally, Antineoplaston A10 resists the attack of gastric enzymes. In the small intestine, under alkaline conditions, 30% is digested into phenylacetylglutamine (PG) and phenylacetylisoglutaminate (isoPG) in a ratio of approximately 4:1. The mixture of synthetic PG and isoPG in a 4:1 ratio, dissolved in sterile water constitutes Antineoplaston A10 IV injection. Further metabolism of Antineoplaston A10 results in phenylacetate (PN). Both metabolites PG and PN have anticancer activity. The mixture of PN and PG in a 4:1 ratio, dissolved in sterile water constitutes Antineoplaston AS2-1 IV injection. [18]

ANP therapy's mechanism of action differs from that of RT or cytotoxic chemotherapy. Growth of normal cells is controlled by cell cycle progression genes (oncogenes) and by cell cycle arrest genes (tumor suppressor genes). In cancer, alteration of these control genes in malignant cells favors aggressive cell proliferation. Evidence suggests that ANP therapy targets 204 mutated genes in the malignant genome and functions as a "molecular switch" which "turns on" tumor-suppressor genes and "turns off" oncogenes [19, 20]. Hence, the antineoplastic action of ANP therapy in AA involves restoration of cell cycle control, induction of programmed cell death, and interference with cancer cell metabolism and nuclear transport.

Conclusions

Successful completion of Phase I and early Phase II clinical studies led to multiple Phase II clinical studies of ANP therapy in a variety of low- and high-grade brain tumors, including AAs, under the Burzynski Research Institute's (BRI) IND # 43,742. Multiple Phase II protocols have been completed and numerous articles have been published [21-50]. We have presented the case of a 31-year and 11-month-old female with a newly diagnosed AA who obtained a CR and an OS of > 23 years with ANP therapy, suggesting that ANP therapy may be an effective therapeutic option for adults with AA. Further clinical investigation is warranted.

Acknowledgements

The authors express their appreciation to Carolyn Powers for preparation of the manuscript and to Ramiro Rivera, Mohamed Khan, Jennifer Pineda and Adam Golunski for their involvement.

Clinical Trials Registry

ClinicalTrials.gov; ID: NCT00003537

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