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Original Article

Phase II Study of Antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261) in Patients With Recurrent Glioma

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• *Objective*: To assess the pharmacokinetics, toxicity, and efficacy of antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261).

• *Design*: We initiated a phase II trial in order to determine whether evidence of antitumor activity of A10 and AS2-1 could be documented.

• *Material and Methods*: Patients with anaplastic astrocytoma or glioblastoma multiforme recurring after radiation therapy were eligible for enrollment in the trial. Patients received escalating doses of A10 and AS2-1 by multiple intermittent intravenous injections with use of a portable programmable pump to the target daily dose of 1.0 g/kg for A10 and of 0.4 g/kg for AS2-1.

• *Results*: Nine patients were treated, in six of whom the treatment response was assessable in accordance with protocol stipulations. No patient demonstrated tumor regression. Reversible grade 2 or 3 neurocortical toxicity, consisting of transient somnolence, confusion, and exacerbation of an underlying seizure disorder, was noted in five patients. Mean steady-state plasma concentrations of phenylacetate and phenylacetylglutamine after escalation to the target doses of A10 and AS2-1 were 177 ± 101 μg/mL and 302 ± 102 μg/mL, respectively. Patients who exhibited confusion tended to have higher phenylacetate levels.

• *Conclusion*: Although we could not confirm any tumor regression in patients in this study, the small sample size precludes definitive conclusions about treatment efficacy. Antineoplaston-related toxicity was acceptable in most patients with appropriate dose modification, although severe neurocortical toxicity may occur. Steady-state plasma concentrations of phenylacetate with use of A10 and AS2-1 were similar to those reported with use of similar doses of phenylacetate alone.

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CT = computed tomographic; HPLC = high-performance liquid chromatographic; MRI = magnetic resonance imaging; PA = phenylacetate; PAG = phenylacetylglutamine

The term "antineoplastons" is used to describe mixtures of peptides, amino acid derivatives, and organic acids that serve as components of a theoretical natural defense system against human cancers and other human diseases.[1] A10 (a 1:4 ratio of phenylacetylisoglutamine and phenylacetylglutamine [PAG]) and AS2-1 (a 1:4 ratio of PAG and phenylacetic acid) are two such antineoplastons (code designations: NSC 648539 and NSC 620261, respectively) used by Burzynski and associates[2] in the treatment of patients with recurrent anaplastic astrocytoma or glioblastoma multiforme. In 1991, a team of researchers from the National Cancer Institute reviewed available clinical information from seven patients selected by Burzynski from his clinical experience. From this review, the investigators determined that presumptive evidence of antitumor activity was available, and the National Cancer Institute proposed that phase II trials be conducted.[3]

In addition, preclinical evidence indicates that phenylacetate (PA) may be an active inhibitor of astrocytic tumor growth, and potential mechanisms have been reported.[4-11] Neither the clinical efficacy nor the pharmacokinetic activity of A10 and AS2-1 with use of the antineoplaston protocol advocated by Burzynski has been studied previously by independent investigators in prospectively designed trials. Therefore, we initiated the following phase II trial in an effort to determine the effectiveness and pharmacokinetics of A10 and AS2-1.

SUBJECTS AND METHODS

Patient Eligibility

Before enrollment in the trial, all patients provided written informed consent. Adult patients with histologic proof of anaplastic astrocytoma or glioblastoma multiforme and computed tomographic (CT) or magnetic resonance imaging (MRI) evidence of tumor growth after radiation therapy

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Table 4.—Summary of Types and Severity of Toxic Effects Associated With Antineoplaston Therapy

Toxicity	No. of patients			
	Grade 1	Grade 2	Grade 3	Total
Neurocortical findings	1	2	3	6
Headache	1	...	2	3
Nausea ± vomiting	3	2	1	6
Anorexia	1	...	...	1
Edema	2	1	...	3
Allergic reaction	...	1	...	1
Thrombocytopenia	3	...	...	3
Dizziness or light-headedness	2	...	...	2
Fatigue	2	...	...	2
Myalgia	2	...	...	2
Neurosensory effects	1	...	...	1
Urinary hesitancy	1	...	...	1
Leukopenia	1	...	...	1

Efficacy

Three patients (cases 2, 5, and 6) had reoperation for tumor after treatment with antineoplastons (Table 5). Pathologic examination revealed recurrent tumor in one patient (case 2), recurrent tumor plus radionecrosis in one (case 5), and only radionecrosis in one (case 6). Because this last patient underwent stereotactic radiosurgery before antineoplaston therapy, he is considered ineligible for response assessment. None of the six assessable patients (or three ineligible patients) exhibited CT or MRI scan evidence of tumor regression associated with antineoplaston treatment.

All six assessable patients had scan evidence of tumor progression during antineoplaston treatment ranging from 16 to 66 days, after which treatment was discontinued. Three patients (cases 3, 4, and 7) discontinued treatment because of toxicity, and follow-up scans obtained 16, 16, and 15 days later, respectively, revealed tumor progression. The mean time to treatment failure (either progression or unacceptable toxicity) was 29 days, and the mean time to tumor progression was 33 days (Table 2).

Survival

All nine patients died. The median and mean survival times were 5.2 and 7.2 months, respectively. One patient (case 5) died of sepsis related to complications of chemotherapy administered after discontinuation of antineoplaston treatment. All other study patients died of tumor progression.

Pharmacologic Studies

We assessed the pharmacokinetics of PA and PAG in all nine patients who received antineoplastons by the intermittent infusion schedule outlined in Table 1. Antineoplaston dosages were increased stepwise from the starting level of 0.24 g/kg daily for A10 and 0.12 g/kg daily for AS2-1 to the target level of 1.0 g/kg daily for A10 and 0.4 g/kg daily for AS2-1 during a 4-day period. After 24-hour administration of 0.48 g/kg daily of A10 and 0.24 g/kg daily of AS2-1 (level 2), the mean plasma concentrations (± standard deviations) of PA and PAG were 47 ± 20 µg/mL and 109 ± 37 µg/mL, respectively. Steady-state plasma concentrations of PA and PAG were achieved after 24-hour administration of the target level of 1.0 g/kg daily of A10 and 0.4 g/kg daily of AS2-1. The mean plasma concentrations of PA and PAG were 177 ± 101 µg/mL and 302 ± 102 µg/mL, respectively. Low steady-state plasma concentrations (14 to 35 µg/mL) of phenylacetylisoglutamine were noted in two patients who also had phenylacetylisoglutamine determined during administration of antineoplastons. The plasma concentrations of PA decreased by 30% and 67%, respectively, in the two patients who had their doses of A10 and AS2-1 reduced because of toxicity.

The urinary excretion of PA and PAG was determined in all nine patients. Minimal PA (1% or less) was detected in urine during the collection intervals. Substantial amounts of PAG were recovered in the urine. When recovery was calculated on the basis of total doses of A10 and AS2-1 administered during the collection period, the amount of PAG in the urine represented approximately 100% recovery of the administered PAG and PA.

Immunologic Studies

Four patients had quantitative determinations of B lymphocytes and T lymphocytes at baseline and on day 8 of treatment. No patient exhibited substantial changes in total lymphocytes or any subset, including T lymphocytes,