Minutes of the Meeting of the NCI's Decision Network Regarding Antineoplastons A10 and AS2-1

December 2, 1991

B. Candidates for DN Stage IV

Antineoplastons A10 and AS2-1, NSCs 648539D and 620261/#2

The antineoplastons have been considered an unconventional method of cancer treatment because there have been very few independent interpretable scientific data on their potential clinical efficacy. Based on a recent report of observed responses in brain cancer patients treated with antineoplastons at the Burzynski Research Institute (founded by Dr. S.R. Burzynski) in Houston, Texas, the Cancer Therapy Evaluation Program (CTEP) conducted a site visit to review a "best case" series of clinical responses to antineoplastons in the treatment of brain tumors at that Institute. This case series does not constitute a clinical trial; the cases were selected on the basis of positive response from many different studies of antineoplaston treatment at the Institute. The site visit team determined that antitumor activity was documented in this best case series and that the conduct of Phase II trials was indicated to determine the response rate. The antineoplastons were presented as DN Stage IV candidates for the conduct of Phase II trials in glioblastoma multiforme, anaplastic astrocytoma, pediatric brain tumors, and low-grade gliomas, to confirm the observations in brain tumors at the Burzynski Institute. It was proposed that the same treatment regimen as that used at the Institute would be used in the Phase II trials. A decision regarding subsequent trials (e.g., other tumors, additional Phase I development, Phase III trials in brain tumors) would be deferred until the results of these initial trials were known. If the antineoplastons are approved for Phase II study, Dr. Burzynski will provide supplies of the materials for the clinical trials to the NCI free of charge.

Dr. Burzynski presented background on antineoplaston research. His research is based on the hypothesis that antineoplastons are components of a biochemical defense system against cancer. The antineoplastons are medium and small size peptides and amino acid derivatives that form the defense against cancer by inducing differentiation in neoplastic cells. Initial study on antineoplastons was concentrated on isolation of peptides in blood and urine of healthy people.

Two main groups of antineoplastons have been isolated -- one including compounds with broad spectrum activity in many different cell lines and the other with a narrow spectrum of activity against single cell lines. Of the broad-spectrum antineoplastons, five, including antineoplastons A1, A2, A3, A4, and A5, have been isolated from normal human urine. Antineoplaston A10 was the first active ingredient that has been reproduced synthetically. Antineoplaston AS2-1 and AS2-5 are metabolites of antineoplaston A10 that have also been synthesized. Dr. Burzynski cited experiments that have shown that antineoplaston A10 intercalates in a stereospecific manner between base pairs in double-helical DNA. The main mechanism of action of antineoplaston AS2-1 appears to be inhibition of incorporation of glutamine into proteins in cancer cells. The other antineoplastons all seem to have different mechanisms of action involving inhibition of methylation of RNA and DNA.

The potency of the antineoplastons has been confirmed in tissue cultures, but with relatively low specificity. No significant activity was seen in NCI tissue culture studies when low concentrations were used. Tests in various models for induction of cell differentiation (e.g., human promyelocytic leukemia, fibrosarcoma) showed that antineoplastons can induce cell differentiation. Antineoplastons also showed activity against human breast cancer in athymic mice.

Acute and chronic toxicity studies of antineoplastons showed that antineoplastons A10 and AS2-1 have extremely low toxicity. The LD_{50} of antineoplaston A10 was greater than 10 g/kg in mice and rats; the LD_{50} of AS2-1 was approximately 3 g/kg in mice and rats. There was no apparent toxicity in mice given daily injections of 1 g/kg/day for 1 year. The compounds were not found to be mutagenic.

PK studies of both the oral and injectable forms of antineoplastons A10 and AS2-1 showed that both compounds are absorbed rapidly. The maximum concentration of AS2-1 can be detected in urine approximately 3 hours after oral administration. A10 is absorbed somewhat

slower, reaching the highest concentration in blood approximately 3 hours after oral administration. The compounds are cleared more rapidly after i.v. administration; A10 cannot be detected in the blood approximately 2 hours after i.v. administration. Thus, frequent dosing or continuous infusions is indicated for clinical studies.

From studies in mice, it was also noted that antineoplaston A10 is retained in brain tissue. A concentration of approximately 500 μg/g of brain tissue in mice was reached about 1 hour after oral administration; however, the concentration dropped to a negligible amount within about 6 hours.

A review of the best case series of seven patients with brain tumors was provided by Dr. N. Patronas (neuroradiologist, NIH Clinical Center) who participated in the NCI site visit to the Burzynski Institute. All patients received a combination of antineoplastons A10 and AS2-1. Some patients initially progressed on a study using oral antineoplastons with low-dose methotrexate. All of the responses were seen after i.v. antineoplaston administration, and, therefore, the proposed Phase II studies would be conducted using the i.v. regimen (i.e., 1 g/kg/day of A10 and 0.5 g/kg/day of AS2-1). The results of the review were presented as follows, with case histories distributed to all DNC members:

- Marked decrease in tumor size and possible complete response (CR) of approximately 4-months' duration in a 46-year-old female with glioblastoma multiforme.
- Possible CR, thus far of 2-years' duration, in a 36-year-old female with anaplastic astrocytoma.
- Partial response, or possible CR, in a 47-year-old male with aggressive, infiltrating glioma (astrocytoma or mixed astrocytoma/oligodendroglioma).
- Substantial decrease in tumor size in 7-year-old male with well-differentiated astrocytoma.

- Decrease in tumor size in a 40-year-old female with an unusually large glioblastoma multiforme tumor.
- CR, thus far of approximately 1½-years' duration, in a 10-year-old male with anaplastic astrocytoma.
- Good response, possible CR, in a 30-year-old male with anaplastic astrocytoma.

It was noted that several of the patients received antineoplaston treatment shortly after failing radiation therapy, and the question of the possibility of a confounding effect of residual continued improvement following radiotherapy on evaluating response to antineoplastons was raised. However, complete resolution of both postradiation edema and tumor enhancement was demonstrated on CT scans in several cases, therefore negating the possible problem of differentiating between progression of tumor and postradiation edema.

In discussion, it was clarified that the proposed Phase II trials would utilize the combination of antineoplastons A10 and AS2-1, without any other therapy. No problems were foreseen with filing the INDA on the pharmaceutical preparation provided by Dr. Burzynski. The primary rationale for using a mixture of the two antineoplastons in the proposed trials is to duplicate exactly the regimen used in the studies at the Burzynski Institute.

Decision: Antineoplastons A10 (NSC 648539D) and AS2-1 (NSC 620261/#2) passed DN Stage IV.