The Longwood Herbal Task Force
(http://www.mcp.edu/herbal/default.htm) and
The Center for Holistic Pediatric Education and Research

Antineoplastons

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Summary

Antineoplastons are amino acids, peptides and organic acids developed by an American cancer researcher in the late 1970's. They are among the most well known alternative therapies for patients in whom other therapies have not led to remission. Data from *in vitro* and animal studies, human case series and Phase I trials are promising, but randomized, controlled trials have not been reported. Side effects tend to be milder than with other chemotherapeutic regimens, but may include a broad range of systemic effects such as fever, chills, fatigue, palpitations, weakness, rash and an unusual body odor. No studies have evaluated the use of antineoplastons during pregnancy, lactation or childhood.

Historical and Popular Uses

In the 1970's, a chemist working at Baylor College of Medicine, Stanislaw Burzynski, found compounds in the blood and urine of healthy adults that were absent in the blood and urine of cancer patients. He developed the hypothesis that these peptide fractions could trigger normal differentiation and apoptosis in neoplastic cells and that their deficiency in cancer patients contributed to disease progression[1]. He called these peptide fractions antineoplastons[2].

Burzynski theorized that antineoplastons form the backbone of an innate biochemical defense system (BDS) against cancer that parallels the immune system[3]. The BDS is composed of peptides, amino acid derivatives and organic acids (antineoplastons) which act to reprogram rather than engulf or destroy defective cells. Antineoplastons are hypothesized to be species specific, making animal model testing of human antineoplastons virtually impossible. In 1980, Burzynski identified the chemical structures of antineoplastons, and began preparing them synthetically rather than from human urine. Because of the long political and scientific battles faced by Burzynski, much of the subsequent research on antineoplastons has occurred in Japan

and Europe. Antineoplastons have become a well-known cancer remedy, though access to treatment with them is relatively limited in the United States. In recent years, antineoplastons have also been used to treat other conditions, such as Parkinson's disease, sickle cell anemia and thalassemia[4].

Botany

Not applicable.

Biochemistry

Antineoplastons consist of peptides, amino acid derivatives and organic acids. There are two primary classes of antineoplastons: those with *broad spectrum* activity and those with *selective* activity[5].

a. *Broad spectrum activity*
   i. isolated from urine: A1, A2, A3, A4, A5, A10, A10-1
   ii. synthetically produced: AS10, AS10-1, AS2-1, AS5, AS2-5 (derivatives of glutamine, isoglutamine and phenylacetate)

b. *Selective activity:* H, L, O, F, Ch and K

Burzynski theorizes that AS2-1, AS2-5, AS5 and AS10-1 inhibit the incorporation of glutamine into the proteins of neoplastic cells[6]. Since most neoplastic cells require glutamine to make the transition from G1 phase of cell division to S phase, these antineoplastons arrest cell division at the G1 phase. Further, phenylacetic acid, A2, A3, A5, AS5 and AS2-1 inhibit methylation of nucleic acids in cancer cells, leading to terminal differentiation due to DNA hypomethylation[7,8]. A10 intercalates in DNA directly, possibly alleviating mutagenic DNA sequences containing adjacent pyrimidines[9].

Antineoplaston A10 is 3-phenylacetylamino-2,6-piperidinedione which bears structural and chemical similarities to deoxythymidine and uridine[10]. It was the first antineoplaston chemically identified. When administered orally, it is hydrolyzed by pancreatic enzymes to phenylacetylglutamine (PAG) and phenylacetylisoglutamine (PAIG) which are both water soluble and tend to be further degraded to phenylacetic acid (PAA), which tends to be most stable chemically at pH 4 and is very unstable in alkaline conditions[11,12,13]. All three

breakdown products have anti-tumor effects. The injectable formulation of antineoplaston A10 is composed of PAG and PAIG in a 4 to 1 ratio. A10 is thought to help reduce the excretion of endogenous antineoplastons, thereby enhancing innate defenses[14].

The injectable formulation of *antineoplaston AS2-1* is composed of PAG and PAA in a 1:4 ratio. A10 has cytostatic inhibitory effects; AS2-1 has differentiation-inducing effects, inhibits cell proliferation and induces apoptosis in various tumor cell lines *in vitro*[12]. Physiologic studies of antineoplaston AS2-1 suggest it competes with glutamine for trans-cellular membrane transport, thereby restricting the supply of this amino acid for intracellular processes including mitosis[6].

Experimental Studies

Antineoplastons: Potential Clinical Benefits

1. Cardiovascular: none
2. Pulmonary: none
3. Renal and electrolyte balance: none
4. Gastrointestinal/hepatic: none
5. Neuro-psychiatric: Parkinson's disease
6. Endocrine: none
7. Hematologic: Sickle cell anemia and thalassemia
8. Rheumatologic: none
9. Reproductive: none
10. Immune modulation: none
11. Antimicrobial: none
12. Anti-neoplastic: Antitumor effects, reduction of symptoms associated with cancer and its treatment
13. Anti-oxidant: none
14. Skin and mucus membranes: none
15. Other/miscellaneous: none

1. **Cardiovascular**: none
2. **Pulmonary**: none
3. **Renal and electrolyte balance**: none
4. **Gastrointestinal/hepatic**: none
5. **Neuro-psychiatric**: Parkinson's disease. In clinical trials of antineoplaston A5 for patients with advanced cancer who also suffered from Parkinson's disease, marked improvements in Parkinsonian symptomatology were noted. It was theorized that the antineoplaston provided support for degenerating dopaminergic neurons centrally.
   i. *In vitro data:* none
   ii. *Animal data:* In mice and rats given antineoplaston A5 intraperitoneally, there were significant stimulation of central dopaminergic receptors, increased concentrations of dopamine and noradrenaline in the brain and diminished use of both catecholamines[15]. A5 appeared in animal studies to neutralize both hyper- and hypo-activity of central dopaminergic structures[16].
   iii. *Human data:* anecdotal data only
6. **Endocrine**: none
7. **Hematologic**: Sickle cell anemia and thalassemia. Sodium 4-phenylbutyrate increases hemoglobin F (HbF) production in sickle cell and thalassemia patients.
   i. *In vitro data:* none
   ii. *Animal data:* none
   iii. *Human data:* Six patients with sickle cell disease were treated for periods of two weeks to 6 months with 9 – 13 mgs/M2/day of sodium 4-phenylbutyrate by mouth. Four dropped out in less than four weeks due to an inability to take the 30 – 40 tablets daily. Those who persisted for at least three months had significant increases in HbF levels (from roughly 10% to 15%)[17].
8. **Rheumatologic**: none
9. **Reproductive**: none
10. **Immune modulation**: none
11. **Antimicrobial**: none

12. **Anti-neoplastic**: Antitumor effects, reduction of symptoms associated with cancer and its treatment

    a. Antitumor effects

        i. *In vitro data: In vitro,* antineoplastons profoundly inhibited oncogene expression, limited the proliferation of malignant cells and induced terminal differentiation (reversion toward normal cell structure)[18,19]. Studies at the Uniformed Services University found that antineoplaston AS2-1 promoted maturation in leukemia cell lines. Antineoplaston A10 inhibited estradiol-stimulated cell growth in a human breast cell line *in vivo* and *in vitro*[20]; an hydroxylated derivative, p-hydroxy A10, was more potent than A10 and had activity comparable to tamoxifen in inhibiting cell growth *in vitro*[20]. Sodium phenylbutyrate (PB), an aromatic fatty acid, has significant cytostatic and differentiating activity against primary neoplastic myeloid cells, inducing apoptosis *in vitro*[21]. Antineoplaston AS2-1 exhibited cytostatic effects against human hepatocellular carcinoma *in vitro*[22]. The sodium salt of phenylacetate enhanced synergistically lovastatin's growth suppression of human glioblastoma cells[23]. Antineoplaston A5 inhibited squamous cell cancer cell growth in a dose-dependent fashion while increasing the growth rate of normal fibroblast cells[24].

            In vitro studies of hepatocellular carcinoma cell lines (KIM-1) showed dose-dependent inhibition of cell growth by cisplatin (in the 0.5 – 2.0 mcg/ml range) and antineoplaston A10 (in the 4.0 – 8 mg/ml range); combination therapy (0.5 mcg/ml of cisplatin and 6 mg/ml of A10) was more effective than treatment with either single agent at those dosages[25].

        ii. *Animal data:* As predicted based on their species specificity, human antineoplastons proved ineffective in treating P388 mouse leukemia, the standard National Cancer Institute (NCI) screening test for anti-tumor drugs in the early 1980's. However, several animal studies performed at Kurume University in Japan reported that antineoplastons A10 and AS2-1 reduced urethane-induced pulmonary neoplasms, hepatocellular carcinoma and human breast cancer cell growth in nude mice and were synergistic in their effects with standard chemotherapeutic agents[26,27,25]. Studies at the Medical College of Georgia have confirmed A10's ability to prevent the

development of mammary tumors in mice with high rates of spontaneous mammary tumor development and carcinogen-induced tumors[28,29]. Antineoplaston A10 prevented the development of benzo(a)pyrene-induced pulmonary adenomas in mice[30]. *In vivo* studies have suggested that phenylacetate may act synergistically with interferon alpha to inhibit growth and enhance cell differentiation in a variety of lines of human lung adenocarcinoma[31].

iii. *Human data:* As of late 1998, nearly 20 case series and case reports have been published on antineoplastons. As early as 1977, Burzynski reported remissions of advanced cancer or leukemia in 18 of 21 patients treated parenterally with antineoplaston A[32]. In 1988, he reported that 68% of 19 adults with non-metastatic bladder cancer achieved complete remission of their cancers when treated with antineoplastons A, As, A3, A5, A10 and AS2-1[33]. In 1990, he reported a series of 14 patients with advanced prostate cancer whose disease had progressed despite standard surgical, radiation, chemotherapeutic and hormonal therapies who were then treated with antineoplaston AS2-1 and low dose diethylstilbesterol (DES); 2 of the 14 had complete remissions and 3 had partial remissions[34]. In 1991, the NCI reviewed seven of Burzynski's best cases and concluded that anti-tumor effects were achieved.

Case series from investigators in Japan also report promising results. In a series of 3 adult patients with advanced cancer, combination treatment with antineoplastons A10, AS2-1 and standard chemotherapy and radiation were associated with a rapid anti-tumor response[35]. In several cases of adults with liver cancer (hepatocellular carcinoma and multiple liver metastases from colon cancer), AS2-1 was used successfully as maintenance therapy for more than two years following unsuccessful treatment with transcatheter arterial embolization and microwave coagulation necrosis[12,22].

Antineoplaston therapy is not always successful, even in case series. Among patients with several different types of brain tumors treated with standard courses of surgery, radiation and chemotherapy who also received antineoplastons, a complete or partial remission was noted in only three of nine patients[36]. In 75% of the case series evaluating disease response to treatment, over 50% of patients reported

complete remission, partial response, no disease progression or disease stabilization. The Food and Drug Administration (FDA) has approved Phase II studies for patients suffering from breast cancer and several types of brain tumors, including pediatric patients. However, no randomized controlled trials of the effectiveness of antineoplastons have yet been published.

b. Reduction of symptoms associated with cancer and its treatment
   i. *In vitro data:* none
   ii. *Animal data:* none
   iii. *Human data:* A case report of a 16 year old boy who developed hyperammonemia and encephalopathy following high dose chemotherapy for acute lymphoblastic leukemia (ALL) noted improvement with high dose sodium benzoate and phenylacetate, primarily due to their ammonia-trapping properties[37].

13. **Antioxidant:** none
14. **Skin and mucus membranes:** none
15. **Other/miscellaneous:** none

Toxicity and Contraindications

All herbs and nutritional supplements carry the potential for contamination.
Allergic reactions can occur to any natural product in sensitive persons.

Potentially toxic compounds in antineoplastons: Amino acids, peptides

Acute toxicity: Acute toxicity studies of A2 in mice revealed no significant toxicity[38]. Phase I trials in Japan show little toxicity of AS2-1[22]. One unusual side effect noted by patients using antineoplastons is a strong body odor, similar to urine. Other side effects include chills, fever, stomach upset and mild rashes.

Chronic toxicity: Side effects have been noted with all types of antineoplastons given over weeks to years. However, in most cases it is difficult to distinguish effects due to antineoplastons from effects arising from the primary tumor or co-therapies. Researchers who have studied the toxicology of antineoplastons report far less toxicity with them than with other chemotherapeutic agents[39].

In a Phase I trial of antineoplaston A10 given in intravenous doses of 200 – 390 mg/kg-day over 52 –640 days to 18 adults with a variety of advanced cancers, adverse side effects included fever, muscle and joint pain, sore throat, abdominal pain, nausea, dizziness and headache. Desirable effects included increased white blood cell and platelet counts[40]. Oral administration of antineoplaston A10 in 42 patients with various advanced cancers resulted in no significant toxicity reported; four of 42 patients reportedly achieved complete remission[41].

In a phase I trial of antineoplaston AS2-1 given to 20 adults with advanced cancer in doses up to 160 mg/kg-day from 38 – 872 days, side effects were reportedly minimal and included mild electrolyte imbalances (3/20), fever (1/20), nausea and vomiting (1/20), a maculopapular allergic-type rash (1/20)and mildly elevated blood pressure (1/20)[42].

A phase I trial of antineoplaston A2 in 15 adults with advanced, metastatic cancer who were treated by daily intravenous injections for 53 – 358 days reported side effects including fever, chills, and myalgia, none of which were severe enough to discontinue treatment; desirable side effects included increased platelet and white blood cell counts and decreased cholesterol and triglyceride levels[43].

During six months of oral treatment with sodium 4-phenylbutyrate, two of six patients with sickle cells disease developed side effects: rash and ankle edema; myelotoxicity was not observed in any patient[17]. In some patients treated with antineoplastons, increases in white blood cell counts, hematocrit and platelet counts were noted along with decreased levels of triglycerides and cholesterol[41].

In a phase I trial of antineoplaston AS2-5 given to 13 patients with advanced cancer in doses up to 167.6 mg/kg-day from 41 to 436 days, side effects were reportedly mild and included fever (2/13) and swelling of small joints (1/13); eight patients discontinued treatment and three patients died during the trials[44].

A phase I trial of antineoplaston A3 injections in 24 adults with various advanced cancer reported side effects including fever (4/24 patients), vertigo (2/24 patients), headache (2/24), and flushing, nausea and tachycardia in one patient each; reactions were

described as mild and occurred only once during courses of treatment that lasted from 44 – 478 days[45].

A phase I trial of antineoplaston A5 in 15 adults with various types of advanced, metastatic cancer noted adverse effects including fever (5/15 patients), arthralgia (1/15) and palpitations(1/15) over the course of 47 – 130 days of treatment[46].

Phase I studies of antineoplastons given in combination with standard chemotherapy revealed that antineoplaston A10 in doses of 10gms – 40 gms daily over two years and antineoplaston AS2-1 given in doses of 12 gms – 30 gms daily over three years were associated with major adverse effects of fatigue, weakness, myelosuppression and liver dysfunction; these effects were not noted when the antineoplastons were given alone without standard chemotherapy). Minor adverse effects noted with antineoplastons were excessive flatulence, maculopapular rash, headache, palpitations, peripheral edema, vertigo, hypertension, reduced albumin, increased amylase, hypoglycemia, hypokalemia, eosinophilia, and increased alkaline phosphatase. None of these effects was severe enough to discontinue treatment[39,40,42,44].

Limitations during other illnesses or in patients with specific organ dysfunction: Unknown

Interactions with other herbs or pharmaceuticals: Unknown

Safety during pregnancy and/or childhood: Unknown

Typical dosages

Provision of dosage information dose NOT constitute a recommendation or endorsement, but rather indicates the range of doses commonly used.

Doses are given for single agent use and must be adjusted when using remedies in combinations.

Doses may also vary according to the type and severity of the condition treated and individual patient conditions.

Antineoplastons are typically delivered parenterally but are also available in oral preparations

The average treatment (now available in the US only as part of experimental protocols) lasts from 4 – 12 months and may cost from $36,000 - $60,000. Those most commonly used are AS2-1 and A10 given by injection.

Dosages used in combinations: Unknown
Pediatric dosages: Unknown

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