Michael B Schachter MD, CNS

Schachter Center for Complementary Medicine
2 Executive Boulevard
Suite 202
Suffern, New York 10901
Phone: 845-368-4700; FAX: 845-368-4727
Website: www.schachtercenter.com
E-Mail: www.office@mbschachter.com

1

Supporting Body Defenses against Breast Cancer with Avemar & AHCC

8th Annual Complementary Medicine Conference: "A Holistic Approach to Breast Health": SUNY New Paltz, NY
April 19, 2009

2

Disclosures

- Xymogen
  - Board of Advisors
  - Own some shares in company (< 1%)
- American Bioscience Inc.
  - Small honorariums for occasional lectures
- Maitake Products, Inc.
  - Will support trip to Japan with honorarium this summer to lecture about CAIM and Cancer
- Natural Source (Producers of Beljanski products)
  - Rare support for lecture

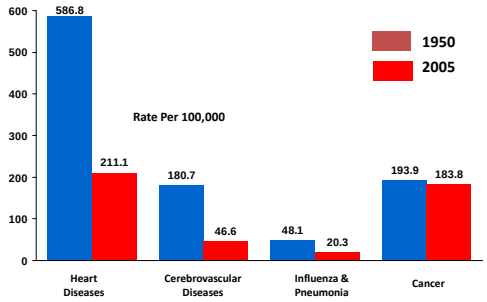
3

Tools

- Available as handouts at the American BioScience booth and at our website: www.schachtercenter.com
  - Brief summary handout of Dr. Schachter's views on Cancer and CAIM
  - Cancer Reading List
  - Cancer Website List
  - Avoid and To Do List

4

Change in the U.S. Death Rates* by Cause: 1950 & 2005



* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2005 Mortality Data: US Mortality Data 2005, NCHS, Centers for Disease Control and Prevention, 2008.

5

Conventional Cancer Therapies for Breast Cancer

- Surgery
- Radiation Therapy
- Chemotherapy
- Hormonal or anti-hormonal therapies (like Tamoxifen, Arimidex or Lupron)
- Monoclonal antibodies inhibit one of the steps of the cancer process (like Herceptin or Avastin); Newest drugs (there are many)

6

Focus of Conventional Cancer Treatment

- Destroy cancer cells with once of conventional treatments
- Not much emphasis on lifestyle, good nutrition
- Patients often told to avoid all nutritional supplements, as they might interfere with conventional treatment
- Measure progress by tumor shrinkage—Not a good measure of progress

7

Goals of Integrative Treatment for Breast Cancer

- Prevent breast cancer
- Help prevent recurrences
- Focus on survival and quality of life
- Support conventional treatment with various methods to improve results and reduce adverse effects of conventional treatment
- Methods emphasize, non-invasive, selective treatments that focus on lifestyle, nutrition, nutritional supplements, exercise, stress management, energy balancing
- Help patients make decisions about conventional treatment

8

Integrative Evaluation of the Cancer Patient

- Focus on patient as a person
- Assess strengths and weaknesses
- Evaluate support system
- Full clinical history & physical examination for many practitioners (MD, DO, PA-C, NP, etc)
- Assess current lifestyle factors
- Assess patient's ability to make changes
- Nutritional and Laboratory testing

9

Integrative Laboratory Testing for the Cancer Patient

- Complete routine labs
- Check certain nutrients levels (especially vitamins A and D, selenium, others)
- Check heavy metal toxicity (levels of lead, cadmium and mercury)
- Check appropriate cancer markers (e.g. CEA, CA19-9, CA27-29)
- Check for immune function

10

Integrative Cancer Therapies May Include-1

- Dietary suggestions-cornerstone-organic food (reduced toxins-increased nutrients-phytonutrients as information)-Quillin-Raw, Live Food Organic diet
- Avoid poor quality food and toxic exposures (See my website: Avoid & To Do List)
- Lifestyle changes-Exercise-Stress Management-Sunlight Exposure-Sleep
- Oral nutritional supplements

11

Integrative Cancer Therapies May Include-2

- Detoxification-Bowel, Liver, Skin, Saunas
- Injectable treatments-C drips, B17
- Energy treatments-Homeopathy, Acupuncture
- Attempt to deal with attitude, stress and spiritual elements
- Help with decisions relating to conventional treatment

12

What Questions a Patient or Support Person Should Ask?

- Likelihood survival time will be increased (Clinical response is NOT so important)
- Likelihood quality of life will be improved
- Risks associated with the treatment:
  - Morbidity
  - Mortality
  - Secondary cancers

13

Example: Standard of Care for Stage I & II Breast Cancer

- Lumpectomy
- Radiation therapy
- Chemotherapy in most cases
- Anti-hormonal therapy if cancer is estrogen receptor positive
- Possible monoclonal therapy drug (like Herceptin) if HER2/Nu positive
- Can look at all of these, but we'll focus on radiation

14

Radiation and the Treatment of Breast Cancer A Cancer Decisions® Report (Ralph Moss)

- Reduces risk of a recurrence in the same breast
- Does NOT reduce regional recurrence or distant metastases
- No impact on overall survival with increased deaths from causes other than breast cancer.
- Harmful effects (e.g. heart damage, lymphedema) may occur later
- See: www.cancerdecisions.com for report

15

Should Radiation be Automatic for Breast Cancer?

- So, should women automatically accept radiation for breast cancer after lumpectomy
- Many breast cancer patients refuse radiation and do intensive integrative program after lumpectomy
- Change the milieu in which cancer developed in the first place

16

Integrative Therapeutic Approach for Cancer Patients

- Go to basics of nature and nurture
- Power of food to harm or heal- overlooked by medical practitioners and consumers alike.
- Role of nutrition in preventing cancer recognized for decades (Thousands of research articles; Recognized: NCI, ACS, AICR)
- But, role in healing cancer—ignored by oncologists-cancer organizations
  - Susan Silberstein PhD; www.beatcancer.org

17

Move Toward Nature

- "Whatsoever is the father of disease, poor diet is the mother." (Chinese Proverb)
- "All mankind needs for health and healing is provided in nature." (Paracelsus, Father of pharmacology)
- "Natural forces within us are the true healers. Let thy food be thy medicine and thy medicine be thy food" Hippocrates: The Father of Medicine

18

Estimates of CA deaths avoidable by dietary change (from NCI)

- Prostate 75%
- Colon/rectum 75%
- Breast 70%
- Endometrium, Gall Bladder 50%
- Stomach 35%

19

Effects of Dietary Change on Diagnosed Cancer

- Avoidance of malnutrition
- Minimization of treatment side effects
- Optimization of cytotoxic effects
- Protection of healthy tissue
- Healthy cell proliferation
- Immune enhancement
- Hormonal changes

20

Epigenetics and Cancer

- Epigenetics refers to how our environment affects gene manifestations
- With cancer pro-cancer genes are switched on and anti-cancer genes are switched off
- The typical American diet upregulates cancer genes and downregulates anticancer genes
- The organic, raw, vegan diet upregulates anti-cancer genes and downregulates procancer genes

21

Supplements for Cancer Patients: Yes or No?

- Selective agents that inhibit or kill cancer cells, but do not harm normal cells
- Treatments that strengthen rather than weaken the body and the body's defenses against cancer
- What about notion that cancer patients should avoid supplements when undergoing radiation or chemotherapy?

22

Chemotherapy & Antioxidant Supplementation-Keith Block MD

- Reviewed 845 peer-reviewed articles
- Identified 19 clinical trials-met strict inclusion criteria.
- Most study participants-advanced or recurrent disease given various supplements.
- Conclusion: "None of the trials reported evidence of significant decreases in efficacy from antioxidant supplementation during chemotherapy."

23

(2) Chemotherapy & Antioxidant Supplementation-Keith Block MD

- Many studies showed that antioxidant supplementation was associated with "increased survival times, increased tumor responses, or both, as well as fewer toxicities than controls"

Block KI, Koch AC, Mead MN, Tothy PK, Newman RA, Gyllenhaal C. Impact of antioxidant supplementation on chemotherapeutic efficacy: A systematic review of the evidence from randomized controlled trials. *Cancer Treat Rev. 2007 Mar 14*

24

Charles Simone MD (Radiation Oncologist and Chemotherapist)

- **"Since the 1970s, 280 peer-reviewed in vitro and in vivo studies, including 50 human studies involving 8,521 patients, 5,081 of whom were given nutrients, have consistently shown that non-prescription antioxidants and other nutrients do not interfere with therapeutic modalities for cancer. Furthermore, they enhance the killing of therapeutic modalities for cancer, decrease their side effects, and protect normal tissue. In 15 human studies, 3,738 patients who took non-prescription antioxidants and other nutrients actually had increased survival."**

25

Charles Simone's References

- Charles B. Simone II, MD; Nicole L. Simone, MD; Victoria Simone, RN; Charles B. Simone, MD. **ANTIOXIDANTS AND OTHER NUTRIENTS DO NOT INTERFERE WITH CHEMOTHERAPY OR RADIATION THERAPY AND CAN INCREASE KILL AND INCREASE SURVIVAL**, PART 1 and 2. *Altern Ther Health Med*. Jan-Feb, and Mar-Apr, 2007;13(1):22-28; 13(2): 40-7.)
- Simone CB, Simone NL, Simone CB II. Oncology Care Augmented with Nutritional and Lifestyle Modification. *J Ortho Mol Med*. 1997; 12(4): 197-206.
- Simone CB. **Cancer and Nutrition, A Ten Point Plan for Prevention and Cancer Life Extension**. Princeton Institute. 2006.

26

Eight Clusters of Procancer Events John Boik

- **1-Gene mutations and genetic instability**
- **2-Gene expression (Switching on and off)**
- **3-Abnormal signal transduction**
- **4-Abnormal cell to cell communication**
- **5-New blood vessel formation-angiogenesis**
- **6-Invasion into tissues**
- **7-Metastasis to other organs**
- **8-Immune suppression and other forms of immune evasion**

Natural Compounds in Cancer Therapy-2001

27

1-Genetic Mutations

- **Proto-oncogenes become oncogenes**
  - **Examples are Ras gene mutations**
  - **Ras gene mutation present in 20 to 30% of human cancers**
  - **Accelerators or promoters of cancers**
- **Tumor suppressor gene mutations**
  - **Example is P53**
  - **Present in about 50% of human cancers**
  - **Brakes or inhibitors of cancers**

In cancer, oncogenes are over-active and tumor suppressor genes are under active

Causes of Mutations

- **Toxic Exposures**
  - **Toxic elements (e.g. lead, mercury, fluoride)**
  - **Organic toxins (e.g. pesticides, chemicals in plastics, xenoestrogens)**
  - **Radiation exposure**
- **Insufficient protective factors**
  - **Lack of antioxidants (e.g. vitamins A, C, E, and minerals such as selenium)**
  - **Sunlight in optimal amounts**

2-Genetic Expression or Turning the Genes On or Off

- **We have 30,000 genes in each cell**
- **Only about 3,000 active at one time**
- **There are switches that turn genes on or off either temporarily or permanently**
- **In cancer, oncogenes are turned on and tumor suppressor genes are turned off**
- **To treat cancer, do the opposite**
- **Burzynski's antineoplastons act as switches to fight cancer**
- **Various phytonutrients found in raw fruits and vegetables do the same thing**

3-Abnormal Signal Transduction

- Cancer cells have abnormally high growth factor receptors (e.g. insulin growth factor)
- Various growth factors stimulate receptors
- Cancer cells produce the growth factors themselves
- Growth signal is transduced by various proteins (e.g. protein tyrosine kinase) to the nucleus to induce rapid growth (like passing a baton)
- Many new monoclonal drugs like Herceptin interfere with one of these transduction steps
- Various natural substances can inhibit this process in various ways (e.g. EPA inhibits protein tyrosine kinase)

Signal transduction is any process by which a biological cell converts one kind of signal or stimulus into another

4-Abnormal Cell to Cell Communication

- Normal cells interact with and control each other via cell adhesion molecules and gap junction communication
- Cancer cells break off communication and behave like renegades
- Various natural substances (e.g. melatonin, Resveratrol) tend to re-establish and normalize communication

5-New Blood Vessel Formation: Angiogenesis

- Cancer requires new blood vessels in order to grow
- Cancer cells produce molecules to stimulate angiogenesis
- Natural substance Angiostatin (modified into a drug is approved for breast cancer treatment)
- Natural substances (e.g. certain proteins from shark cartilage) inhibit angiogenesis
- Copper depletion inhibits angiogenesis

Read the book: *Dr. Folkman's War*- by Robert Cooke for a better understanding

6-Invasion of Tissues

- Cancer cells secrete enzymes to break down the surrounding tissue
- Weakness in the tissues allows this
- Natural substances (e.g. vitamin A, vitamin C and Curcumin) may strengthen the matrix
- Natural substances (e.g. Boswellic acids, Proanthocyanidins from grape seed) inhibit the enzymes that break down the tissue

7-Metastasis

- Cancer cells travel to distance organs and grow
- 5 step process
  - Cell detachment and entrance into bloodstream
  - Migration through the circulation
  - Arrest in a new location
  - Exit from bloodstream into tissues
  - Cell proliferation and new blood vessel formation

7-Metastasis-(cont)

- Immune system may help prevent metastasis
- Platelet aggregation and fibrin production enhance metastasis-allow cancer cells to stick in location
- Natural substances (e.g. proteolytic enzymes, EPA, vitamin E) counteract platelet aggregation and fibrin production

8-Immune Suppression and Other Forms of Immune Evasion

- Immune system plays some role in controlling cancer
- Non-specific mechanisms (e.g. natural killer cells)
- Specific mechanisms (e.g. cytotoxic killer T cells)
- Various natural substances enhance immune function

Killing Cancer Cells: Apoptosis vs. Necrosis

Apoptosis	Necrosis
• Programmed cell death	• Violent cell death
• Individual cells	• Large groups of cells die
• Cell membranes don't rupture	• Cell membranes rupture
• No inflammation	• Inflammation present
• Orderly and preferred	• Disorderly and less desirable

Using Natural Non-Toxic Substances to Prevent and Treat Cancer

- Mild relatives to chemotherapy drugs—30 times less potent in vitro
- About 21 times less toxic than most chemotherapy drugs
- Each substance acts at several steps of cancer process
- Synergistic effects-must be used in combination

U.S. Patent 6,355,474
March 12, 2002

Avemar: A truly remarkable natural product

Development initiated many years ago by Dr. Albert Szent-Gyorgyi, a recipient of the Nobel Prize in Medicine.

Produced by a patented process that yields a uniform, consistent all-natural dietary supplement.

More than 100 reports have been written for presentation or publication describing research conducted in the United States, Hungary, Russia, Austria, Israel and Italy.

Validated by the publication of more than 18 peer-reviewed studies accessible by Medline.

40

History

- Albert Szent-Gyorgyi (Hungarian)
  - Nobel Prize winner for discovering Ascorbic Acid in 1937
  - Loss of wife (breast cancer)
  - Wanted to find a cure for cancer
  - Wheat germ-quinones-and ascorbic acid
- Otto Warburg
  - Cancer specific metabolism of sugars
- Avemar Research-Mate Hidvegi PhD

41

INTRODUCTION

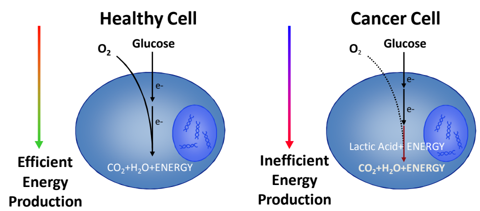
Otto Heinrich Warburg

- Nobel Prize in Physiology or Medicine 1931
  "for his discovery of the nature and mode of action of the respiratory enzyme."

- Cancer cells exhibit increased glycolysis a phenomenon known as the "Warburg effect" and is considered as one of the most fundamental metabolic alterations during malignant transformation.

42

Glucose Metabolism



Oxidative Metabolism: Glucose and oxygen efficiently produce ATP with Carbon dioxide and Water byproducts

Anaerobic Metabolism: Glucose without oxygen inefficiently produces ATP with carbon dioxide, water and lactic acid byproducts

43

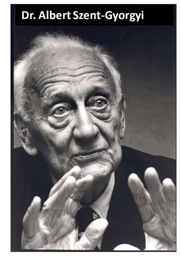
From Nobel Prize …

…to prized supplement

Interest in cancer therapies-revulsion over use of mustard gas derivatives for cancer treatment- battlefield experiences with chemical warfare agents in World War I.

His efforts grew in earnest when both his wife and daughter contracted and died of cancer.

Theorized that naturally occurring compounds called quinones, would suppress anaerobic metabolism in cancer cells and enhance oxidative metabolism in normal cells



1937 Nobel Laureate in Medicine

For his part in the discovery of vitamin C, and the mechanisms of cellular metabolism

44

Early experiments with natural and synthetic forms of DMBQ showed promise and demonstrated the effects that Szent-Gyorgyi predicted, but. . .

…by the 1960's, when his experiments were gaining momentum, the concept of regulating cancer cell metabolism was eclipsed by the view that cancer therapies needed to concentrate on killing cancer, at any cost, and so Szent-Gyorgyi's work was overlooked.

45

Fall of Communism Leads to a Blossoming of Ideas & Initiative

The fall of communism in Hungary liberated scientists from central control, and allowed independent research.

Biochemist Dr. Mate Hidvegi resumed Dr. Szent-Gyorgyi's work, patenting a technique of fermenting wheat germ with baker's yeast to produce a laboratory standard compound for research and later commercialization.

46

Research was promising, but limited by financial constraints, and it seemed that fermented wheat germ might again fade into obscurity.

Being a devout man, Dr. Hidvegi prayed to Mary, Mother of God, for guidance– and an investor.

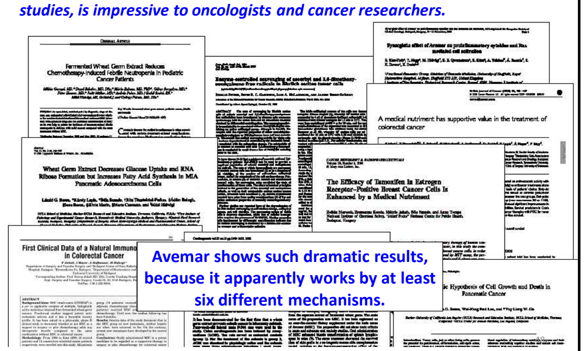
"Avé Maria, if it is your will, that this research should be continued, please send an investor."

The very next day, a stranger who happened to be one of the early entrepreneurs in the new Hungary, offered Dr. Hidvegi the funding he needed.

In thanks, he named his new product "Avemar"

47

Development of Avemar - *The rapid pace of Avemar research, more than 100 studies since 1996, and its scope, involving dozens of researchers, has methodically progressed from cell line to animal studies and to human studies, is impressive to oncologists and cancer researchers.*



Avemar shows such dramatic results, because it apparently works by at least six different mechanisms.

48

Mechanisms of Action of Avemar

- Inhibits glycolysis and enhances aerobic metabolism
- Immune modulation
- Induces apoptosis-programmed cell death
- Anti-angiogenesis
- Anti-metastatic
- Inhibits cancerous DNA synthesis

49

*Research at UCLA using a stable isotope form of glucose shows that Avemar inhibits non-oxidative glucose metabolism

- Reducing the production of RNA and DNA associated with cancer cell proliferation
- Restoring normal pathways of cell metabolism
- Resulting in an increase in the production of RNA and DNA associated with cell differentiation and healthy function

The greater the metastatic potential of the cancer cell line tested:

✓ *The higher the glucose utilization rate*

✓ *The more dramatic Avemar's effect*

A 50 times higher concentration needed to negatively effect normal cells

* Wheat germ extract decreases glucose uptake and RNA ribose formation but increases fatty acid synthesis in MIA pancreatic adenocarcinoma cells. Pancreas 23: 141-147, 2001. *

*Metabolic profiling of cell growth and death in cancer: applications in drug discovery. Drug Discovery Today 7(6), 18-26, 2002.

50

Inducing cancer cell suicide (Apoptosis)

Enhances the mechanisms of programmed cell death in cancer cells (referred to as "apoptosis" or cell suicide) in two complementary ways.

✓ *By inhibiting the production of PARP [poly (ADP-ribose) polymerase], a DNA repair enzyme cancer cells need to reproduce.*

✓ By enhancing the production of Caspase-3, an enzyme that in the absence of PARP initiates programmed cell death.

The mechanism of many anti-cancer therapies (chemotherapy, radiation, and herbal) is to induce programmed cell death, Avemar enhances their effectiveness by lowering the "threshold" of apoptosis.

FWGE inhibits glycolysis/pentose cycle enzymes and induces apoptosis through poly (ADP-ribose) polymerase activation in Jurkat T-cell leukemia tumor cells. J Biol Chem 277: 46408-46414, 2002.

FWGE induces apoptosis and downregulation of major histocompatibility complex class I proteins in tumor T and B cell lines. Int J Oncol 20: 563-570, 2002.

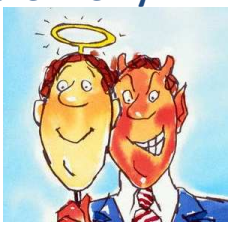
51

Unmasking the Enemy

Avemar helps the immune system identify cancer cells for attack.

Cancer cells try to hide from the immune system's Natural Killer (NK) cells by displaying a surface molecule called MHC-1.

MHC-1 tells NK cells, "don't attack me, I'm one of the good guys,"…



…but, research shows Avemar suppresses cancer's mask (MHC-1) resulting increased NK cell targeting and cancer cell death.

Fermented wheat germ extract induces apoptosis and downregulation of major histocompatibility complex class I proteins in tumor T and B cell lines. Int J Oncol 20: 563-570, 2002.

Avemar triggers apoptosis and downregulation of cell surface MHC I proteins in lymphoid tumor cells. Scientific meeting of the Albert Szent-Györgyi Medical and Pharmaceutical Center of the Szeged University. Szeged, Hungary, 2000.

52

*Proven to support overall immune strength, coordination and function (Adaptogenic)

✓ Enhance Macrophage functioning, stimulating appropriate Tumor Necrosis Factor production and ICAM, a cytokine that enables white blood cells to pass through blood vessel walls and infiltrate tumors.

✓ Improve the ability of T-cells to respond to antigen presentation, and B-cells to respond to activation and produce appropriate antibodies.

✓ Normalize balance of cellular and humoral (Th1/Th2) immune function in the immune system that results from age and stress

*Studies of the effect of Avemar on tumor necrosis factor induced cytotoxicity and on TNF production of immune cells. Institute of Biochemistry, Biological Research Center of the Hungarian Academy of Science. Szeged, 1999

*Effects of Avemar on the early events of the immune response. Institute of Genetics, Biological Research Center of the Hungarian Academy of Science. Szeged, 1999.

*Effect of Avemar on macrophages and microvascular endothelial cells. Scientific meeting of the Albert Szent-Gyorgyi Medical and Pharmaceutical Center of the Szeged University. Szeged, Hungary, 2000.

53

Avemar's safety and toxicological profile is as well researched as its other attributes.

Extensive cell line and animal testing showed no ill effects or toxicity at any level

Results of extensive human testing and follow up with thousands of subjects confirmed Avemar's safety profile.

In the opinion of the independent panel of medical, food safety and toxicology experts that confirmed Avemar's GRAS status with in accordance with FDA regulations,

"Avemar has the toxicological profile of bread."

54

Clinical Studies

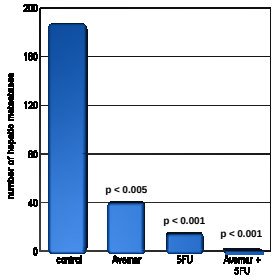
- Anticancer Effect
  - Colorectal
  - Malignant melanoma
  - Oral cavity cancers with metastases to neck
  - Breast cancer
  - Lung cancer
  - Pediatric cancers
- Autoimmune Disorders
  - Rheumatoid arthritis and SLE

55

Methodical progression from *in vitro* and *in vivo* research to clinical trials

- Colorectal Cancer
- Melanoma
- Oral Cancer

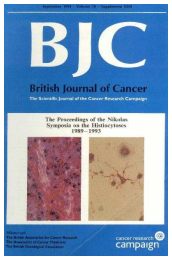
Inhibiting Colorectal Metastases in Mice



- Both Avemar (3 g/kg/d) and 5-Fluorouracil (1 mg/kg/d) significantly reduce the number of liver metastases of C38 colorectal murine carcinoma
- Avemar + 5FU in combination show a still greater efficacy

Cancer Biother Radiopharm 14: 277-289, 1999

*Controlled study of 170 sequential subjects with primary colorectal cancer



Control Group: Surgery and standard of care (chemotherapy, radiation and other appropriate treatment)

Treatment Group: Surgery and standard of care with Avemar, taken once per day (dose 9 grams daily) for 1 year

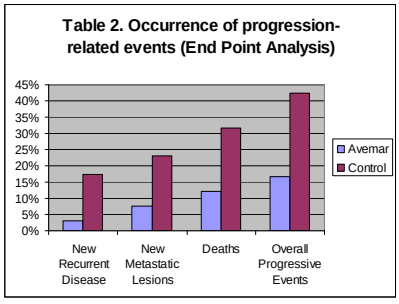
Evaluation at 80 months

- ✓ 82% reduction in new recurrences (p <.01)
- ✓ 67% reduction in metastasis (p <.01)
- ✓ 62% reduction in deaths (p <.01)

*A medical nutriment has supportive value in the treatment of colorectal cancer, *Br J Cancer* 2003 Aug 4;89(3):465-9. (Patients not randomized, but given choice of treatment)

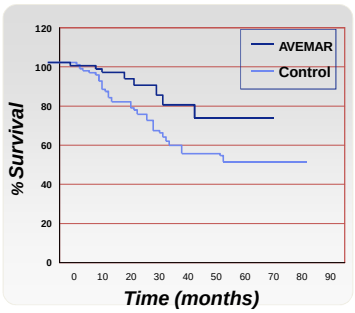
58

Colorectal Cancer–Clinical Trial



British Journal of Cancer (2003), 89:465-469

BJC (2003) Colorectal Cancer Survival probability curve (Kaplan-Meier estimate)



60

Avemar in Metastatic Colorectal Cancer (Israeli Study)

- Double-Blind, Multicenter Clinical Study (Only Double-Blind Randomized Placebo Study)
- Dept of Medical Oncology; Chaim Sheba Medical Center; University of Tel-Aviv
- Gastrointestinal Cancers Unit; Department of Medical Oncology; Ichilov Medical Center; University of Tel-Aviv

61

All the patients had UICC Stage IV colorectal cancer with inoperable distant metastases

- AVEMAR group: 21 patients (16 males and 5 females) Mean age: 66.3 years (47-84 years)
- Placebo group: 15 patients (6 M and 9 F) Mean age: 62.9 years (52-76 years)

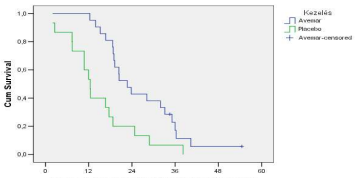
AVEMAR group: irinotecan (Campto) plus AVEMAR
Placebo group: irinotecan (Campto) plus placebo

62

Kaplan-Meier survival analysis
Computed from the first occurrence of the metastatic disease

	Survival time median (months)	95 % confidence interval of the median of the survival time
AVEMAR	22.7	17.6 – 27.9
Placebo	12.4	10.2 – 14.6

Survival Functions



Survival from the first occurrence of the metastatic disease (months)

Log Rank test p=0.04
Survival of the patients in the Avemar group is significantly longer than that in the placebo group.

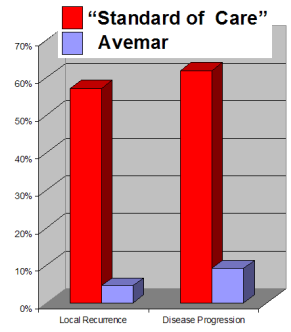
63

*Oral Cancer (squamous cell carcinomas, stage II, III and IV)

Non-Randomized, 43 patients comparing 21 patients as historical controls receiving surgery and "standard of care", with 22 patients receiving "standard of care" plus Avemar for 1 year

Conclusion: Avemar reduced the risk of overall progression at one year by 85% (2 vs 17) and new recurrence (1 vs 12)

At 5 years, survival was 74% in Avemar group and 45.2% Controls



*A medical nutriment has supportive effect in oral cancer, (unpublished , Márta Ujpál, et.al.)

64

AVEMAR in Head and Neck Cancer

N= 45 (44 planocellular, 1 adeno cc)

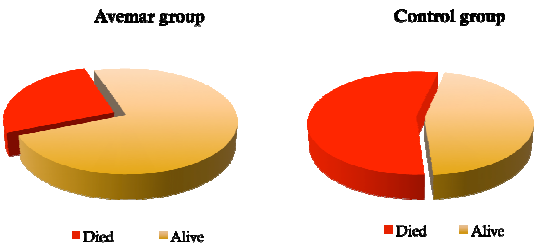
Results – after 1 year

	AVEMAR®	Control	
Mortality	0/23	1/22	N.S.
New recurrence	1 (4.3%)	12 (54.5%)	p<0.001
New metastasis	1 (4.3%)	4 (22.7%)	N.S.
Progression event	2 (8.7%)	17 (77.3%)	p<0.001

AVEMAR in Head and Neck Cancer

N= 45 (44 planocellular, 1 adeno cc)

Results – *after 5 years*



Melanoma metastases in Mice

Treatment	Number of lung metastases average±SD
Control group	20,0±6,0
MSC 3g/kg/day p.o.	4,0±2,1*
DTIC 60 mg/kg/day i.p.	7,0±4,3*
MSC+DTIC	0,1±0,1**

*<0,01

**p<0,001

Figure 5. Effect of the therapeutic composition (MSC+DTIC) on the number of lung metastases of B16 melanoma inoculated into the muscle of the hind leg.

Treatment	Spleen mass (g) ±SD (SEM)	Liver mass (g) ±SD (SEM)	Number of metastases ±SD (SEM)
Control group	0,84± 0,32 (0,11)	0,61± 0,35 (0,12)	185± 104 (35)
MSC 3g/kg/day p.o.	0,86± 0,25 (0,08)	1,14 ±0,19 (0,06)	41± 34 (11)*
5FU 1 mg/kg/2 days i.p.	0,26 ±0,13 (0,04)	1,09+ 0,36 (0,12)	16±17 (6)**
5FU+MSC	0,12 ±1,02 (0,008)	1,04± 0,21 (0,07)	2± 4 (1)**

*p<0,003

**p<0,001

Figure 6. Effect of the therapeutic composition (MSC+5FU) on liver metastases of C38 colorectal carcinoma and on the mass of the parent tumor containing spleen.

MSC – code name for Avemar, fermented wheat germ extract

Avemar as Adjuvant in Stage III Melanoma

Cancer Biotherapy and Radiopharm, August, 2008

- **Site: Blokhin Cancer Center of the Russian Medical Academy, Moscow**
- **Design: open, prospective, randomized Phase II**
- **Objective: Avemar's effects on disease outcome in high-risk melanoma patients**
- **Follow-up: 7 years**

Table 3. Survivals of stage III cutaneous melanoma patients.

	Groups	FWGE	Control
	Number of patients	26	26
	Patients without progression	15 (57.7%)	7 (26.9%)
Progression-free survival (PFS)[3]	Median [CI[1]] (months)	See note[2]	8.5 [7.2-9.8]
	Mean [CI] (months)	55.8 [39.8-71.7]	29.9 [15.3-44.5]
	Patients alive	17 (65.4%)	10 (38.5%)
Overall survival (OS)[4]	Median [CI[1]] (months)	See note[2]	25.7 [11.3-40.1]
	Mean [CI] (months)	66.2 [53.1 79.4]	44.7 [30.2 59.2]
	5-year survival rate (%)	61.5	36.7

[1] 95% confidential interval.
[2] Median can not be defined if the cumulative survival ratio is less than 50%.
[3] Log Rank–test: chi-square [1] = 6.08; P = 0.0137
[4] Log Rank–test: chi-square [1] = 4.72; P = 0.0298

Enhancing quality of life in Ca patients

Many natural and nutritional therapies are regarded as supportive therapies, and are not studied for their direct effect on tumors.

Instead they are evaluated for benefits in terms of preventing or reversing cancer therapy related side effects and improving quality of life.

Several studies of this type have been conducted with Avemar.

71

Solid Cancers for Children

- **15 year-survival: Now 90% compared to 30%**
- **Avemar reduce complications so that kids could receive more chemotherapy to help cure rate**

72

Avemar helped to prevent the chemotherapy induced suppression of immune function that lead to the life threatening opportunistic infections in children with cancer treated with chemotherapy.

	Control	Avemar	% Improvement
Chemotherapy Cycles per patient	9.6	11	n/a
# of Febrile Neutropenic Events (FNE) per Patient	4.2	2.7	35.71%
Average Days Duration of FNE	8.9	6.1	31.46%
Frequency of FNE	43.40%	24.80%	42.86%

(Incidents of Febrile Neutropenic Events (FNE) are associated with infections & high fever that necessitate early termination of therapy)

***Fermented Wheat Germ Extract Reduces Chemotherapy-Induced Febrile Neutropenia in Pediatric Cancer Patients, J Pediatr Hematol Oncol 26 (10), October 2004.**

73

Avemar helped reduce side effects associated with chemotherapy and improve quality of life.

Breast Cancer

55 women with breast cancer under chemotherapy treatment studied over 3 years, showed the use of **Avemar** was associated with **improvement in symptoms of fatigue, insomnia, nausea, vomiting and constipation, and in measures of global health, physical and emotional function**. 1

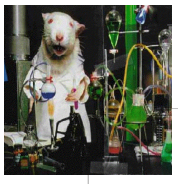
39 women with breast cancer under chemotherapy treatment studied over 1.5 years, showed Avemar improved or eliminated side effect symptoms in the majority resulting in weight gain. 2

Lung Cancer

17 men and women with lung cancer under chemo and radiation treatment studied over 8 months, showed daily use of Avemar resulted in improvement in measures of fatigue, social function and global health. 3

1.Effects Of Long-Term Avemar® Treatment On Quality Of Life In Breast Cancer, Balogh A, et al, 2001 (Unpublished).
2.Supportive Effects Of Avemar® In Breast Cancer, Balogh A, et al, 2001 (Unpublished)
3.Effects Of Avemar® Treatment On Quality Of Life In Terminal Lung Cancer, Ajkay Z, et al, 2000 (unpublished).

***Avemar shown to have cancer preventive effect**

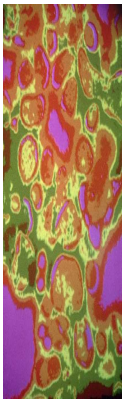


Avemar's ability to prevent cancer is suggested by experiments in animals, the F344 rat, where chemical induced colon cancer was inhibited by 58% compared with animals that were not fed Avemar.

	Percent animals with colon tumors	Average number of colon tumors per animal	Average diameter of tumors (cm)	Total tumor area (cm2)
Control (n=10)	0%	0	n/a	n/a
Carcinogen only (n=47)	**83%**	**2.3+/-.021**	**2.35+/-.25**	**4.85+/-.43**
Carcinogen + Avemar	**45%**	**1.3+/-.17**	**2.21+/-.12**	**2.03+/-.28**
Avemar Only	0%	0	n/a	n/a
Reduction due to Avemar	**46%**	**43%**	**6%**	**58%**

*** Wheat germ extract inhibits experimental colon carcinogenesis in F-344 rats. *Carcinogenesis* 22: 1649-1652, 2001.***

75



Effective against all cancer cell lines tested

Test tube (in vitro) studies of cell lines in culture, and animal (in vivo) studies of implanted tumors have demonstrated Avemar's anti-cancer effects against every cell line tested

Lung cancer

Pancreatic

Lymphoma

Leukemia

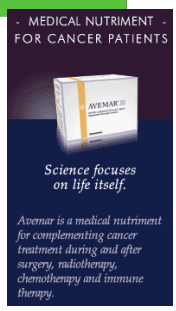
Breast cancer (estrogen positive, negative and inflammatory)

Prostate

…And others

76

In Hungary Avemar is approved as "a medical food for patients with cancer," and physicians throughout the country have reported favorable results in many tumor types, in thousands of patients.



metastatic **ovarian** cancer

metastatic **gastric** cancer

metastatic **thyroid** cancer

metastatic **non-Hodgkin's lymphoma**

metastatic **multiple myeloma**

metastatic **hepatocellular** carcinoma (liver cancer)

metastatic **prostate** cancer

metastatic **breast** cancer

metastatic **non-small cell lung** cancer

77

Additional Avemar Research

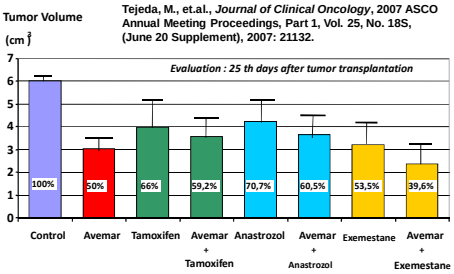
- **ASCO 2007 Annual Meeting – Effect of Avemar on the Growth of MXT Breast Cancer Carcinoma**
- **Effect of Avemar on Estrogen Receptor Positive and Negative Tumor Model**
- **Effect of Avemar on the Growth of Pc-3 Human Prostate Tumor Xenograph in Mice**

78

2007 American Society of Clinical Oncology "FWGE Inhibits Mammary Carcinoma"

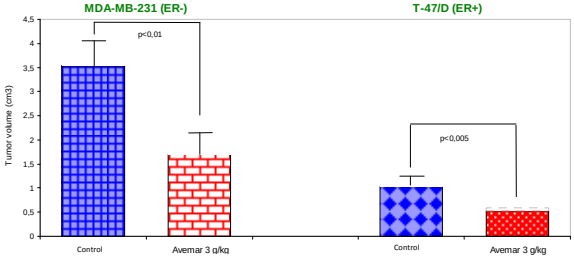
Influence of AVEMAR on the tumor inhibitory effect of Tamoxifen Aromatase inhibitor compounds applying in combined treatments

Tejeda, M., et.al., *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings, Part 1, Vol. 25, No. 18S, (June 20 Supplement), 2007: 21132.



79

EFFECT OF AVEMAR ON ESTROGEN RECEPTOR POSITIVE AND NEGATIVE TUMOR IN XENOGRAFT MODEL



Evaluation 48 days after tumor transplantation

Telekes et al

80

Avemar with Implanted Breast Cancers in Animals

- Avemar worked at least as well in inhibiting cancer growth as any anti-estrogen
- Only one combination with Avemar was better than Avemar alone
- Avemar worked with estrogen negative cancers as well, whereas anti-estrogens did not work at all

81

Drug Interactions

- Cytostatics
  - Increases efficacy of all tested chemo agents
  - Decreases side effects and toxicity
  - Reduces neutropenic septicemia
- Increases the efficacy of anti-estrogens
- Could be administered with cytokines
- Synergistic with Imatinib mesylate (Gleevec Used in Chronic Myelogenous Leukemia or CML) and antagonizes resistance
- Ascorbic acid may attenuate the effect of Avemar and should be taken at orally at least 2 hours away from it.

82

Summary

- Avemar inhibits cancer specific metabolism using multiple modes of action
- Synergistic with cytostatics
- Efficacy (in clinical studies) colorectal and oral cavity cancer, melanoma
- Decrease in febrile neutropenia episodes
- Improvement of QOL
- No adverse health effects
- Available for patients in need

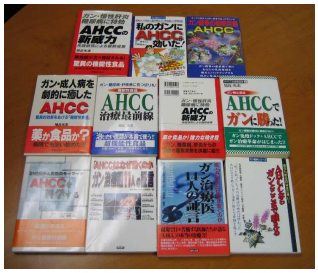
83

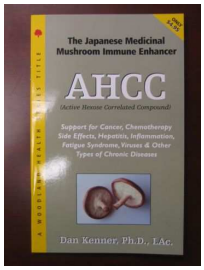
Avemar: Administration & Cost

- One box = 1 month supply, 30 packets per box
- Each packet contains 17g of powder, 8.5g of Avemar Pulvis, 9g of low glycemic fructose, naturally orange flavored
- Take one packet per day, preferably 2 hours away from food, medication or other supplements
- Retail Price: $199.95 Per Month, $6.67 Per Day
- Generally, not covered by insurance

84

Active Hexose Correlated Complex (AHCC)





85

Active Hexose Correlated Compound (AHCC)

- Naturally-derived complex compound:
  - Created by reacting specific enzymes with
  - Several subspecies of hybridized medicinal mushrooms
- Unique compound formed through proprietary cultivation method and a patented manufacturing process
  - Not a mushroom complex
  - Low molecular weight of 5,000 Daltons as compared to other immune ingredients

  (rice bran, beta-glucans and standard mushroom extracts are usually ~200,000 Daltons)

86

Active Hexose Correlated Compound (AHCC) 2

- Biological response modifier with strong immunomodulating properties
- Shown in scientific research to increase activity of white blood cells
  - White blood cells protect against & destroy abnormal cells (viruses, bacteria, parasites)
  - Increased activity of Natural Killer (NK), B, B Helper, Killer T, Lymphokine Activated Killer (LAK) cells, Macrophage and Cytokines

87

AHCC Production Facility

Sapporo, Japan

88

The Case for AHCC

- Supported by over 100 studies
  - Over 4,000 patients have been involved in clinical trials
  - Researched by over 30 prestigious institutions worldwide
  - New studies presented annually at the AHCC Research Symposium
- Used in over 700 clinics worldwide
- Over 17 years of use in Japan and 6 years in the U.S.
- #1 Selling Immune Supplement in Japan
- Subject of more than 10 books in Japan
- Won multiple recognitions including Nutracon Best Product (2002)

89

AHCC Research in the U.S.A.

- Univ. of Texas, Anderson Cancer Center
- University of California, Davis Cancer Center
- Brigham and Women's Hospital (Harvard)
- Faulkner Hospital (Harvard)
- Columbia Presbyterian (Holistic Urology)
- Yale School of Medicine, Rheumatology
- SUNY Binghamton, Biological Sciences
- University of Texas, Houston Medical, Surgery
- Drexel University, Bioscience and Biotechnology

90

Science and Research behind AHCC

91

The Immune System - Physiology

- Complicated series of cells that include:
  - Natural killer (NK-cells)
  - Macrophages
  - T and B cells
  - Substances they release
    - Histamines
    - Leukotrienes
    - Others
    - Cytokines
    - Interleukins
    - Mast cells

92

Misfiring of the Immune System

- Assault on the immune systems causes:
  - Decreased functioning of the natural killer (NK) cells
  - Decreased functioning of the T-cells and macrophages
  - Suppression of IL-2
  - Overproduction of IL-6 and other inflammatory cytokines
- Long-term impact: chronic illness
- Immune system: key health and should be a key focus of preventive medicine

93

Natural Killer Cells

- Serves a dual function
  - Cytotoxic destroyer
  - Immunoregulator
- Sentinel cells
  - First line of defense against invading pathogens (viruses, bacteria, cancer cells)
- Critical Role of NK cells
  - Cancer sells are produced continuously in the body
  - NK cells must remove them before they multiply

Proper functioning of NK cells is critical to human health

94

AHCC and NK Cells

- Increases NK cell activity by 300-fold
  - Stimulates T-cells
  - Stimulates Macrophages
  - Stimulates Cytokines
- Appears to be able to stimulate and modulate
  - Works on both the macrophages and the cytokines
  - Valuable links and network messengers
- Can work in auto-immune disorders because it does not over-stimulate the immune system
- AHCC has a built-in dampening system
  - Can be taken continuously
  - Does not need to be stopped like other immune-enhancing supplements

95

AHCC improves the Prognosis of Liver Cancer after Surgery

- Although AHCC has shown in In vitro experiments that it enhances natural killer cell activity, the effects of AHCC in a clinical setting have not been reported
- Aim of study was to determine if AHCC can improve the prognosis of hepatocellular carcinoma (HCC) patients following surgical treatment.
- Prospective cohort study was performed from February 1, 1992 to December 31, 2001. A total of 269 consecutive patients with histologically confirmed HCC were studied.
- All of the patients underwent resection of a liver tumor.
- Time to treatment failure (disease recurrence or death) and ten parameters related to liver function after surgery were examined.

96

AHCC improves the Prognosis of Liver Cancer after Surgery-2

- RESULTS: Of the 269 patients, 113 received AHCC orally after undergoing curative surgery (AHCC group). The AHCC group had a significantly longer no recurrence period and an increased overall survival rate when compared to the control group by Cox's multivariate analysis.
- CONCLUSIONS: This study suggests that AHCC intake can improve the prognosis of postoperative HCC patients.

J Hepatol. 2002 Jul;37(1):78-86. Comment in: J Hepatol. 2002 Jul;37(1):147-50. Matsui Y, Uhara J, Satoi S, Kaibori M, Yamada H, Kitade H, Imamura A, Takai S, Kawaguchi Y, Kwon AH, Kamiyama Y. First Department of Surgery, Kansai Medical University, 10-15 Fumizono,Moriguchi, Osaka 570-8507, Japan. matsui@takii.kmu.ac.jp

AHCC Improves Survival in Patients with Advanced Liver Cancer

- Prospective cohort study-44 patients-confirmed liver cancer
- Survival time, quality of life, clinical and immunological parameters related to liver function, cellular immunity, and patient status were determined.
- 34 patients received AHCC and 10 received placebo
- Patients in the AHCC treated-group had a significantly prolonged survival when compared to the control group by Mann-Whitney test (95% CI, p = 0.000).

98

AHCC Improves Survival in Patients with Advanced Liver Cancer-2

- Quality of life in terms of mental stability, general physical health status, and ability to have normal activities were significantly improved after 3 months of AHCC treatment when tested using the Wilcoxon signed-rank test (on one-sided test, p = 0.028, 0.037, and 0.040, respectively).
- Conclusion: AHCC could prolong the survival and improve the QOL-patients with advanced liver cancer

Asian Pac J Allergy Immunol. 2006 Mar;24(1):33-45. Cowawintaweewat S, et al Faculty of Allied Health Sciences, Thammasat University Rangsit Campus,Patumthani, Thailand.]

Adding AHCC to Treat GI & Breast Cancers at Fujimoto Hospital

- Presented at 6th AHCC Symposium (1998) and 8th AHCC Symposium (2000)
- Yusuf Kawaguchi MD, PhD-Asst Prof-Dept of Surgery, Kansai Medical University
- 127 patients with breast or GI cancers (gastric and colon) treated for 3 years and 3 months
- Mean survival rates and mean survival times in several stages improved compared to those average rates in Japan
- Quality of life also improved

100

Addition of AHCC to Breast Cancer Patients Treated at Fujimoto Hosp (6th & 8th AHCC Symp)

Type of Cancer	Stage	Cases No.	Dead/Total	MST (months)	MSR (%)	Average MSR in Japan
Breast	0-I	6	0/6	___	100	___
Breast	II	8	0/8	___	100	____
Breast	III	2	0/2	___	100	70
Breast	IV	4	2/4	30	50	35
				Mean Survival Time	Mean Survival Rate	

101

Addition of AHCC to Gastric Cancer Patients Treated at Fujimoto Hosp (6th & 8th AHCC Symp)

Type of Cancer	Stage	Cases No.	Dead/Total	MST (months)	MSR (%)	Average MSR in Japan
Gastric	0-I	6	0/6	___	100	___
Gastric	II	1	0/1	___	100	____
Gastric	III	6	2/6	27	66.7	35
Gastric	IV	15	2/15	14.4	50	8
				Mean Survival Time	Mean Survival Rate	

102

Addition of AHCC to Colon Cancer Patients Treated at Fujimoto Hosp (6th & 8th AHCC Symp)

Type of Cancer	Stage	Cases No.	Dead/Total	MST (months)	MSR (%)	Average MSR in Japan
Colon	0-I	6	0/6	___	100	___
Gastric	II	1	0/1	___	100	____
Gastric	III	6	2/6	27	66.7	35
Gastric	IV	15	2/15	14.4	50	8
				Mean Survival Time	Mean Survival Rate	

103

Addition of AHCC to Gastric Cancer Patients Treated at Fujimoto Hosp (6th & 8th AHCC Symp)

Type of Cancer	Stage	Cases No.	Dead/Total	MST (months)	MSR (%)	Average MSR in Japan
Colon	0-I	2	0/2	___	100	___
Colon	II	8	0/8	___	100	____
Colon	III	18	2/18	10.2	89.9	55.9
Colon	IV	14	10/14	13.1	28.6	21.0
				Mean Survival Time	Mean Survival Rate	

104

AHCC + Chemo UFT Reduces Metastases in Rat Breast Cancer

- Combination had some effect on primary cancer growth and some metastatic expression
- In vitro, combo increased NK Cell activity, whereas UFT alone depressed NK
- So, benefits of AHCC with chemo mediated by immune enhancement

Matsushita K et. a. Anti-Cancer Drugs 1998, 343-350.

105

AHCC Potential for Chemotherapy Drug Interactions

- AHCC: potential for drug-drug interactions involving CYP450 2D6, such as doxorubicin (Adriamycin) or ondansetron (Zofran-used to treat nausea with chemo)
- Safe to administer with most other chemotherapy agents that are not metabolized via the CYP450 2D6 pathway
- J Soc Integr Oncol. 2008 Summer;6(3):105-9. Mach CM, Fugii H, Wakame K, Smith J. Division of Pharmacy, The University of Texas M.D. Anderson Cancer Center, Houston, TX

106

AHCC Reduces Cisplatin Evoked Adverse Effects in Tumor-Bearing Mice

- Enhanced cisplatin-induced antitumor effect in both the size ($p<0.05$) and weight ($p<0.05$)
- Increased the food intake in the cisplatin-treated mice.
- Reduced kidney damage
- Reduced bone marrow due to cisplatin

Toxicol Appl Pharmacol. 2007 Jul 15;222(2):152-8. Epub 2007 Apr 20. Hirose A, et al

107

AHCC Enhances Tumor Surveillance to Prevent Cancer in Mice

- Potential role of AHCC in tumor immune surveillance is unknown
- C57BL/6 mice were given AHCC or water followed by tumor cell inoculation.
- AHCC treatment significantly delayed tumor development after inoculation of either melanoma cell line B16F0 or lymphoma cell line EL4.

108

AHCC Enhances Tumor Surveillance to Prevent Cancer in Mice-2

- Enhanced both Ag-specific activation and proliferation of CD4(+) and CD8(+) T cells, increased the number of tumor Ag-specific CD8(+) T cells, and more importantly, increased the frequency of tumor Ag-specific IFN-gamma producing CD8(+) T cells.
- Increased Natural Killer cells, improving the function of these innate-like lymphocytes.
- Conclusion: AHCC can enhance tumor immune surveillance through regulating both innate and adaptive immune responses.

2006 Oct;55(10):1258-66. Epub 2005 Dec 16. Active hexose correlated compound enhances tumor surveillance through regulating both innate and adaptive immune responses. Gao Y, Zhang D, Sun B, Fujii H, Kosuna K, Yin Z. Section of Rheumatology, Department of Medicine, Yale School of Medicine

AHCC Cancer-Related Research

- Used in Asia and the U.S. to reduce side-effects of chemotherapy
  - Reduce toxicity
  - Improve quality of life
- Research supports the following modes of action:
  - Increases Tumor Necrosis Factor
  - Increases Gamma Interferon
  - Increases IL-12 (all decrease when undergoing chemotherapy)
  - Decreases circulating level of IAP (Immuno-suppressive acidic protein)
  - Decreases circulating level of IAP and TGF-B (tumor growth factor–Beta)
- Multiple Studies in Japan for this Indication
  - On formulary in over 700 hospitals as adjunct to Chemotherapy and Radiation Therapy
  - Increasingly used in the U.S. with very positive reported results

110

Other Uses of AHCC in Clinical Practice

Modulation of the cytokine defense mechanism

- Allergies
- Asthma
- Chronic Sinusitis
- Eczema
- Fibromyalgia
- Hives
- Rashes
- Seasonal Disorders
- Hepatitis C-Liver Disorders

Raise CD-4 counts an important immune system cellular component

- Post-Chemotherapy
- HIV
- Lyme Disease
- Chronic Fatigue
- Osteoarthritis
- Cold and Flu Prevention
- Cold and Flu Treatment

"AHCC might be used as a daily supplement for the immune system, along with a multivitamin"

111

Why AHCC is a Useful Nutritional Supplement

- Offers an effective balance between high levels of stimulation of the NK cell mediated pathways
- Documented clinical and basic science research at prestigious hospitals around the world
- Documented efficacy studies
- Significant anecdotal evidence / positive response of patients
- Documented safety studies
- No toxicity
- Very few and rare side-effects

112

Usage and Dosage

- Available as 500 mg Capsules
- Therapeutic Dosage
  - Patients with highly comprised immune systems
  - Recommended therapeutic dose: 1 gram (2 capsules) 3 times daily
- Preventive Dosage
  - Health-conscious adults seeking to heighten their immune activity
  - Recommended preventive/therapeutic does 500mg – 1g daily (1 to 2 capsules daily

113

Summary for AHCC

- Biological Response Modifier with strong immunomodulating properties
- Extensive clinical research
- Strong safety data
- Significant clinical usage
- Helpful for patients with:
  - Immune disorders
  - Liver disease
  - Cancer
  - Undergoing chemotherapy
  - Chronic illnesses
  - Illnesses directly caused by inflammation
- Important for prevention of lifestyle diseases

114

Take Home Messages

- All women should be on a cancer (and other degenerative disease preventive program
- Offered a number of tools to help develop this program
- Women with current breast cancer or a history of breast cancer particularly should be on an intensive program
- Diet is key to any preventive program

Take Home Messages-2

- Women should be careful about decisions regarding conventional cancer treatment
- Nutritional supplements can be very helpful as part of a program
- Two supplements (Avemar and AHCC) have been discussed in some depth
- Because of complementary mechanisms, they should be useful when taken together, though no clinical research on the two together is available