

Curing Cancer's Sweet Tooth By Dr. Frank Ervolino

Both doctors and cancer researchers alike have dreamed of developing an anti-cancer therapy that would target only cancerous cells and spare healthy cells. Even today's cutting edge targeted cell therapies have had side effects ranging from minor to mortal. There is a compound available that is used in Europe, kills cancer cells by a variety of mechanisms, targets kinases responsible for cancer cell death and differentiation, has a specific effect on molecular targets for cancer and works with ER+ or ER- cancers and has shown to be effective in colon cancer, melanoma, pancreatic cancer lymphoma and leukemia.

One of the most compelling adjunctive cancer therapy stories has to do with the way cancer cells use glucose.

More than 80 years ago Nobel laureate Otto Warburg showed that cancer cells altered basic cell metabolism that involved using glucose to produce energy. The modification involved using glucose in a less efficient way than the oxidative phosphorylation method preferred by normal cells. Cancer Cells instead use Glycolysis which involves the less efficient lactic acid pathway. Doctor Warburg theorized that cancer was caused by altered cellular metabolism. It is now common knowledge that cancer cells use far more glucose than healthy cells of the body. Healthy cells of the body use glucose mainly for energy production via the Krebs cycle using oxygen in what is called the oxidative pathway. Cancer cells use up to 50 times the amount of glucose used by healthy cells in a process that needs no oxygen. This non-oxidative pathway is called glycolysis and cancer cells use it to fuel the synthesis of DNA and RNA. This happens even in the presence of oxygen which usually prevents glycolysis and it is thought that cancer cells do this to survive in oxygen deprived states as the growing tumor moves farther from its blood supply. This ability of cancer cells to use the non-oxidative pathway even in the presence of oxygen is called the Warburg effect. It is unfortunate that in the pursuit of medical research power sometimes is in the hands of those who do not have the foresight to recognize genius if it is not their own. Like Pasteur did with Koch's work, fellow Nobel Laureate Hans Krebs dismissed Otto Warburg's theory as a symptom of cancer but not the primary cause. While he may have had a point what was lost in all this was the significance of the implications in the treatment of cancer that could come from Dr Warburg's work. Now, more than 70 years later scientists are reexamining Dr. Warburg's work in the interest of finding new strategies that will benefit all those who may have to get treatment for cancer. What they are looking at is that to combat cancer it would be wise to be able to downregulate or discourage the non-oxidative pathway for glucose metabolism used by cancer cells and upregulate the oxidative pathway our healthy cells use to generate energy in our bodies. Chemotherapy doesn't do this, radiation therapy doesn't and neither does the new cutting edge targeted cell therapies, but it turns out there has been a compound available that does this and it has been used in Europe for many years. It is called Avemar in this country and it has quite a remarkable story.

What is Avemar?

Avemar is an aqueous or water based extract of the fermentation of wheat with *Saccharomyces cerevisiae* for 18 hours at 30°C. This is done because the active biochemical constituents of Avemar, 2,6-dimethoxy-benzoquinone (DMBQ) and 2-methoxy-benzoquinone need to be released from their glycoside form as they are found in the raw wheat. In the glycoside form they are not as effective. This form of yeast extraction is widely used today in mainstream pharmaceutical applications and consumer items such as the brewing of beer.(20)

After the fermentation process is complete, the liquid is decanted, spray-dried, micro-encapsulated, homogenized and formulated to yield a dried extract that is standardized to contain methoxy-substituted benzoquinones (2-methoxy-benzoquinone and 2,6-DMBQ) at a concentration of 0.04%. Because it is an aqueous extraction it does not contain the gluten and gliadin found in wheat products. The fermentation process does not extract these components. So the wheat plus the yeast yields a fermented liquid that frees the benzoquinones found in glycoside form in wheat to yield DMBQ.(21) Quinones are found in many plants and several of them have exhibited anti-cancer properties, but they are fragile compounds that easily combine when taken with food, alcohol or other plants. The problem is that when they combine with other substances they lose their anti-cancer properties. This means that many plant based quinones that have anti-cancer properties in the lab lose them when made into a commercial product. Avemar is presented as a pure DMBQ extract and taken away from food or other substances to ensure clinical effectiveness. It is important to note that even though the extract does not contain gluten or gliadin, it does come in contact with these substances so people with sensitivities to wheat should use caution with Avemar.

Avemar from a Historical Perspective

Dr. Albert Szent-Gyorgyi is responsible for taking Otto Warburg's work and giving it a practical application in the fight against cancer. In 1937, he received the Nobel Prize himself for his work in discovering vitamin C. The substances in wheat germ that Szent-Gyorgyi had identified proved able to stop the proliferation of malignant cells. Initial experiments showed this occurred partly because the extract restricted malignant cells' access to the large amounts of glucose they required to grow and divide. It interfered with growth because glucose is the source of energy for growth. It interfered with cell division of malignant cells (but not normal cells) because it interfered with transketolase (TK), an enzyme malignant cells use in the non-oxidative pathway to make the nucleic acid ribose for DNA and RNA of new cells. When cells cannot proceed in an orderly fashion through the growth and division phases of the cell cycle, they are forced into apoptosis – the programmed cell death that protects the body from development of abnormal cells.

Unfortunately, Dr Szent-Gyorgyi's work stopped along with his death. The Hungarian biochemist Dr. Máté Hidvégi resumed Dr. Szent-Györgyi's work, developing and patenting a technique of fermenting wheat germ with baker's yeast to produce a laboratory-standardized compound for research and later commercialization.

Avemar Studies for Specific Cancers

In the treatment of T-cell and B-cell Lymphoma it was shown that Avemar increased cancer cell apoptosis resulting in increased cancer cell death.(17) In this cell line study it was interesting to note that Avemar when introduced to the lymphoma cell lines that apoptosis was prominent to a level of 20-48% within 24 hour. It was also noted that MSC did not induce a similar degree of apoptosis in healthy peripheral blood mononuclear cells.(17) This study also showed that Avemar downregulated MHC-1, and promoted apoptosis of tumor cells by affecting tyrosine phosphorylation and Ca²⁺ influx. This is very similar to newer targeted therapies used today.

Decreasing MHC-1 was shown to be effective treatment of in vitro T-cell and B-cell Lymphoma cell lines. it was shown that Avemar increased cancer cell apoptosis resulting in increased cancer cell death acts on lymphoid tumor cells by reducing MHC class I expression.(7) By reducing MHC class 1 the lymphoma cell becomes more susceptible to NK cell activity. NK cell activity is one of the human body's primary mechanisms against cancer.

In the treatment of myeloid leukemia and human cervical cancer cell lines the fermented wheat germ extract found in Avemar induced increased expression of ICAM-1 a cytokine which allows white blood cells to leave the circulatory system and infiltrate tumor cells. Cancerous tumor cells typically have low concentrations of ICAM-1 which protects them from white blood cell infiltration and destruction. The fermented wheat germ extract found in Avemar also increased leukemia cell apoptosis and impaired leukemia cell metabolism through caspase mediated proteolysis of poly(ADP-ribose). Activities of glucose-6-phosphate dehydrogenase and transketolase were inhibited as well. This means there is less ribose available for the RNA and DNA cancer cells need to proliferate and remain viable. This shows the cell growth-controlling and apoptosis-inducing effects of fermented wheat germ. (9)

Avemar showed effectiveness in the treatment of HT-29 human colon carcinoma cell line. It induced both necrosis at a rate of 28% and apoptosis at a rate of 22%. Avemar inhibited the cell-cycle progression, the activity of ribonucleotide reductase which is crucial for cancer cell DNA synthesis, and the activity of cyclooxygenase-1 and -2. In a 170 patient study with post-surgical colorectal cancer patients also receiving standard of care therapy such as chemotherapy, and/or radiation, the group who had Avemar added to their treatment regimen experienced an 82% improvement in new recurrences: 3.0 vs 17.3%, P<0.01 over the control group. The rate of metastases improved by 67%: 7.6 vs 23.1%, P<0.01. The death rate improved by 62%: 12.1 vs 31.7%, P<0.01. Survival analysis showed significant improvements in the Avemar group regarding progression-free (P=0.0184) and overall survivals (P=0.0278) probabilities.(13)

A study on the treatment of ER+ breast cancer showed that when Avemar was added to a Tamoxifen treatment regimen more cancer cells were killed than by Tamoxifen therapy alone. This was achieved by increased cancer cell apoptosis. Avemar strongly enhanced apoptosis of MCF-7 cells 24 and 48 hours after treatment. This enhancement of apoptosis was even greater in cells treated with a combination of Avemar and the estrogen receptor modulator Tamoxifen.(14) This is the study that caused the Sloan-Kettering Cancer Institute to advise caution for ER+ patients when using Avemar. That is because in this study it was shown that Avemar enhanced estrogen-receptor activity of MCF-7 cells. Sloan-Kettering failed to mention that using Avemar and Tamoxifen together further decreased ER+ receptor activity to a degree greater than Tamoxifen alone. The ability to induce cancer cell apoptosis and act synergistically with Tamoxifen outweighs the increase in ER+ receptor activity.

In a clinical study on fermented wheat germ extract in the supportive treatment of squamous cell carcinoma of the oral cavity done with a 5 year follow up, the group using fermented wheat germ extract had a 5 year survival rate of 74% (17 pts) versus the control group survival rate of 45.5% with a $p < 0.05$.(12) This is study that has been submitted for publication. In this study which was non-randomized, there were 43 patients with stage III and IV squamous cell carcinoma. 21 patients were historical controls receiving surgery and “standard of care”. They were compared to 22 patients receiving “standard of care” plus Avemar for 1 year. The study showed that the Avemar group experienced an 85% reduced risk of cancer progression.(12)

In a study done at the UCLA School of Medicine, it was shown that the fermented wheat germ extract found in Avemar interfered significantly with pancreatic cancer cells metabolism. This resulted in a decreased ability of the pancreatic cancer cells to propagate new tumor cells. It also decreased the cancer cells chances of survival.(8) This study was designed to give insight into the mechanism of action of Avemar. Nonetheless it showed that Avemar was effective with pancreatic cancer cell lines.

In an open-label, pilot-scale, randomized, controlled, phase II clinical study to test the possible value of supportive therapy with Avemar in high-risk patients with stage III melanoma of the skin, The Avemar plus DTIC (Dacarbazine) group showed significantly less progression-related events than the DTIC alone group. Progression-free survival and the time to progression was better in the Avemar plus DTIC group. The Avemar plus DTIC group also showed fewer side effects than in those of the DTIC-only group.(10)

Avemar can be used to support the immune system of pediatric patients undergoing chemotherapy for solid tumor malignancies. It was found that Avemar reduced the number of low white blood cell count incidences.(19) It is reasonable to assume that this demonstrates Avemar’s immune stimulating properties to adults as well.

Avemar features

- A study published at the 2007 ASCO (American Society of Clinical Oncologists) meeting, demonstrated that Avemar inhibited the growth of ER+ (estrogen receptor positive) breast cancer more successfully than the world's best selling cancer drug, tamoxifen and better than the antiestrogen therapies Examestane (Aromasin) and Anastrasol. The rate of tumor growth suppression for Avemar was 50%. When Avemar was combined with Examestane (26%), Anastrasol (25%) or Tamoxifen (42%) the efficacy or effectiveness increased by 3-10% demonstrating that Avemar works synergistically with these therapies. What is important to note is that it suppressed tumor growth at a rate higher than the leading hospital cancer therapies.(4)
- In studies of estrogen negative breast cancers, where Tamoxifen and other anti-estrogen therapies are ineffective, Avemar was effective because the mechanism of action for Avemar is independent of hormone status.(4)
- Avemar inhibits non-oxidative glucose metabolism, which is a characteristic alluded to earlier in this article and shared by all cancers.(5)
- Avemar inhibits kinase activity of 16 kinases many of which are known to participate in cell cycle, cell migration, apoptosis and signal transduction. This is similar in action to lapitinib and sunitinib.(1)(2)(3)(9)
- Avemar upregulates healthy, oxidative glucose metabolism, enhancing the function of kinases and genes associated with cell repair and differentiation.
- It makes cancer cells behave more like normal, healthy cells, and therefore more responsive to the anti-cancer effects of various chemotherapy, hormone and radiation therapies, and to the cancer controlling mechanisms of the immune system.(14)(16)
- Avemar has a specific effect on molecular targets such as glucose-6-phosphate dehydrogenase (G6PDH), transketolase (TK) and the activity of ribonucleotide reductase. It inhibits activity at these targets which slows ribose production leading to decreased DNA production which is what cancer needs to stay viable. These molecular targets happen to be the same as for the new frontline targeted therapies being developed now.(17)(18)
- Avemar encourages the apoptosis or death of cancer cells by inhibiting Poly(ADP-ribose) polymerase (PARP), stimulates caspase-3 and increase calcium (Ca-2) influx into cytosol of cells.(13)

Avemar discussion

The new cutting edge drugs that target specific cancer cell sites have limitations in that they are targeting mutated cells that are still undergoing further mutation and adaptation. This could result in different cell receptor site architecture which would render the therapy useless. Avemar does not depend upon cell site specificity to be effective. While it does affect specific kinases by both inhibition and upregulation, it can also interrupt the ability of the cancer cell to use glucose via the non-oxidative pathway as the Warburg effect demonstrated. The genes, cell target sites and enzymes that used in the Warburg

effect are not subject to mutation, but constants that are needed for cancer cell survival which allows Avemar to be effective even in the presence of future cancer cell mutations. Tumor cells have been found to avoid destruction natural killer (NK) cells by overexpression of major histocompatibility complex class I (MHC class I) antigen on the cell surface. Avemar decreases MHC-1 expression making the tumor cells more susceptible to NK cell activity.(7)

Is Avemar safe?

In my experience using Ave with clients, I have found it is well tolerated by most people. No serious side effects have been reported in either the extensive clinical history or in human testing. Occasional burping, bloating or soft stools may occur when first starting with Avemar, but these symptoms usually improve with continued use.

Can I take Avemar during treatment?

Yes, Avemar was shown in research to mitigate side effects of standard cancer treatments as well as increase conventional chemotherapeutic effectiveness by 3-10%. The fermented wheat germ extract found in Avemar was found in research to improve neutropenia or low white blood cells which can allow treatment to continue without interruption.(19)

Avemar was also found not to increase the toxicity or the effectiveness of cytotoxic drugs when used in combination with Dacarbazine, 5-fluorouracyl, or Adriblastina in vitro and Endoxan, Navelbine, and doxorubicin in vivo. (22)

Avemar suggested usage

As a dietary supplement, recommended usage is one Avemar packet per day, mixed with 8 oz (240 ml) cold water (or any other beverage containing less than 10 mg of vitamin C). Mixing is best accomplished by shaking in a closed container (add liquid first, then Avemar, close lid and shake). It is best to consume within 30 minutes of mixing. Avemar should be consumed one hour before or after a meal, and two hours before or after any drugs or other dietary supplements. For best results use Avemar daily.

For people over 200 lbs, the recommendation is to use two packets per day. Consult with a healthcare professional for recommended usage levels for children, and for guidance on alternative usage levels, and use in combination with other dietary supplements.

If diarrhea occurs, try dividing the daily usage amount into two halves, and taking separately, one morning, one late afternoon.

For more Frequently Asked Questions go to
<http://avemarus.com/faqs.html#AveIngredients>

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Dr. Ervolino is a licensed acupuncturist and naturopathic doctor. He practices at Palm Beach Holistic Center in Jupiter. He is vice-chair of the Florida State Board of Acupuncture and on the staff of Jupiter Medical Center. Dr Ervolino attended Bastyr University. More articles and contact information are available at his website www.drervolino.com