

Experimental and clinical results with Avemar (a dried extract from fermented weath germ) in animal cancer models and in cancer patients

MICHELE NICHELATTI, M.D., MÁTÉ HIDVÉGI, M.D.

Avemar Research Group, Limbiate (MI), Italy and Biomedicina Co., Budapest

INTRODUCTION Relationships between food and health today must be studied by taking into account the expanding role of dietary supplements, specialised medical foods and functional foods, collectively named as nutraceuticals. Nonnutrient biologically active components of foods are receiving increasing scientific attention. Health professionals, consumers and industry are incorporating this new knowledge into their own practice, behavior and strategies. In most cases, nutraceuticals can challenge the standard distinctions existing between foods and drugs.

The family of dietary supplements includes not only essential nutrients but also botanical and herbal products, which offer a particular challenge in evaluation of biological activity, active constituents, and interactions with conventional medicines. Medical foods include a somewhat limited category of foods targeted to existing health problems. Functional foods represent an emerging category of food products with claims to offer health benefits. There is a great need for ongoing research and documentation regarding the efficacy, safety, and regulation of both dietary supplements and the other specialized food products. Health professionals need to actively follow these scientific advances to be credible sources of information for their patients (1-2).

Beyond allowed cancer-related health claims, patients are today invested by popular press and advertising with a confusing array of remedies found in dietary supplements and bioactive substances found in foods. Included are specific foods (tomatoes, broccoli, sprouts, chili peppers, yogurt, soybeans), drinks (green tea, grapefruit and orange juice), vitamins (C, D, E, folic acid and beta-carotene), minerals (selenium, calcium)

and some nonnutrient substances like echinacea, saw palmetto, rosemary, cat's claw, mistletoe, kombucha, shiitake mushrooms, and shark cartilage. Most of these compounds are being studied with some relation to cancer; however, the reality is that not long after any information is publicized, patients start self-experimenting with these remedies. They self-dose at a range of levels, both high and low; with consequences that may prove effective, useless, or harmful results.

In the late 1990's, reports were published about a biotech process by which a fermented wheat germ extract could be produced. The product, called Avemar, available as a water soluble granulate for oral consumption, has gained much attention from cancer researchers of several countries, like Israel, Hungary, the United States, England and Russia. The reason why this extract has got so much dedication from researchers was possibly the fact that it has been produced from one of the most common food sources of mankind, and it has shown a good synergism with some anticancer drugs used in standard clinical protocols.

Wheat kernel contains 2-4% germ (also called embryo), which is separated from the endosperm by milling operations like rolling, sieving, etc. In the wheat grain, most nutrients with the exception of starch, are concentrated in the germ. Even though it is nutritious, wheat germ is mainly used as an animal feed. Besides its proteins of high biological value and its oil (showing a good fatty acid pattern), wheat germ is the richest known natural source of tocopherols and also abundant in B-group vitamins. The most significant antinutrients of wheat germ are the lectin WGA (wheat germ agglutinin) and a group of trypsin inhibitors, which can be destroyed by heat treatment. Other remarkable nonnutrients of wheat germ are the bioquinones which are present as glycosides of the corresponding methoxyhydroquinones (3), whose potential anticancer effects have been firstly investigated in experimental systems by Nobel laureate Albert Szent-Györgyi (4).

A group of chemists has produced a per os applicable standardized complex of multiple, biologically active molecules

Levelezési cím:

Dr. med. habil. Hidvégi Máté

Biomedicina Rt.

1137 Budapest, Szent István park 18.

Távbeszélő: (36 1) 266 1023 Távmasoló: (36 1) 266 1026

Villanyposta: hidvegi@biomedicina.com

obtained from the aqueous extract of fermented wheat germ (5). The standardized extract – named as Avemar – has been registered and is now marketed as an over-the-counter dietary supplement in various countries, like Hungary, Israel, Italy, Austria, Slovakia, Czech, Cyprus and Switzerland. It is therefore to point out that Avemar is not a drug, nor an alternative to standard anticancer drugs or standard therapies: Avemar is a dietary supplement to be given to cancer patients to help drugs to work better.

As any natural product, Avemar exerts several biological effects, which can be theoretically explained, according to some possible metabolic modeling (6-7). In general, the biological activity of Avemar can be divided in effects useful for the treatment of neoplastic diseases (8-16) and effects which can be well used in the treatment of certain immune disturbances (17-19). Avemar even improves the patients' quality of life which latter effects can be independent from the previous ones.

ANIMAL EXPERIMENTS: SINGLE USE OF AVEMAR In all experiments, 8-10 week-old inbred mice of 20-22 g body weight were used. The following transplantable tumor lines, grown on mice or rats, were used in the experiments: a highly metastatic variant of Lewis lung carcinoma (3LL-HH), B16 mouse melanoma, C38 mouse colorectal tumor and HCR-25, a human colon carcinoma xenograft (17). In all experiments, Avemar treatment was started 24 hours after tumor implantation. Avemar was dissolved in water and administered by means of a gastric tube. The daily dose was 3 g/kg body weight per os administered in 0.1 ml of water. Control animals received tap water daily (0.1 mL), also via gastric tube.

Avemar treatment resulted in a statistically significant 71% decrease in the number of liver metastases of the 3LL-HH tumor inoculated into the spleen (17). In case of the HCR-25 human colon carcinoma, the 50 days of Avemar treatment decreased the amount of liver metastases, in addition to reducing the weight of the tumorous spleen. The number of metastases in the Avemar-treated animals as compared to the control group was around 50% (17). In case of the B16 melanoma inoculated into the muscle, also a significant decrease of 85% was observed in the number of metastases as compared to the control group (17).

ANIMAL EXPERIMENTS: COMBINED USE OF AVEMAR AND CYTOSTATICS In these experiments the B16 mouse melanoma and C38 mouse colorectal tumor strains were used. The aim of these experiments was to find out how the daily treatment with Avemar (3 g/kg body weight) would influence the tumor growth and metastasis inhibiting effect of treatment with some of the well known antineoplastic agents 5-Fluorouracil (5-FU) and Dacarbazine (DTIC), which are widely used in clinical oncology in the frame of various treatment protocols (17).

The B16 melanoma was used as muscle-lung metastasis model, while the C38 mouse colorectal carcinoma cell line was applied for serving as spleen-liver metastasis model. Mice bearing the C38 colorectal carcinoma implanted into the spleen were treated with 5-FU administered via intraperitoneal injection 3 times a week in a dosage of 1 mg/kg, while the mice inoculated with the B16 melanoma received DTIC treatment daily (60 mg/kg i.p.) Synchronously, the animals treated with antineoplastic agents also received Avemar daily (3 g/kg). In the case of combined (Avemar + DTIC) treatment the number of lung metastases of B16 melanoma practically decreased to zero, and this effect was significant. The results show that in therapeutic composition, Avemar – having metastasis inhibitory effect also alone – exerted a more than additive effect, that is, it synergically enhanced the metastasis inhibitory effect of DTIC used in clinical practice to decrease metastasis in protocols for treatment of patients with melanoma. Treatment of C38 colorectal carcinoma with the therapeutic composition of Avemar and 5-FU decreased the number of liver metastases synergically. This effect was also significant. The mass of the diseased spleen also displayed a marked decrease as a consequence of the treatment.

Although the therapeutic effects at both of the combination experiments were considerable, the usual toxic side effects of cytostatics, e.g. decrease of body mass were not observed. It can be concluded that Avemar treatment does not reduce the antitumoral effects of chemotherapeutic drugs upon the primary tumors but, dramatically enhances their antimetastatic effects. Using several other cytostatics (data not shown) it was also proved that Avemar did not reduce their cytostatic effects upon the primary tumors.

CHEMOPREVENTIVE EFFECTS OF AVEMAR It has been demonstrated that Avemar treatment prevents colon cancer in laboratory animals; in this case, four weeks old inbred male F-344 rats were used (9). Colon carcinogenesis has been induced by injections of azoxymethane (AOM), a well-known carcinogenic chemical. Ten rats served as untreated controls (group 1). For the treatment of the animals in group 2, AOM was dissolved in physiologic saline and the animals were given 3 subcutaneous injections 1 week apart, 15 mg/kg body weight (BW) each. In two additional groups the basal diet was supplemented with Avemar. The extract was dissolved in water and was given at a dose of 3 g/kg BW once a day. In group 3, animals started to receive Avemar two weeks prior to the first injection of AOM daily and continuously thereafter until sacrificed 32 weeks later. In group 4 the basal diet was supplemented by Avemar administration only. At the end of the experiment all the rats were sacrificed by exsanguination, the abdominal large vessels were cut under a light ether anaesthesia and a complete autopsy was performed. The percentage of animals developing colon tumors and the number of tumors per animals were: 0 and 0 (group 1); 83.0 and 2.3 (group 2); 44.8 ($p < 0.001$) and 1.3 ($p < 0.004$) (group 3); 0 and 0 (group

4); all the tumors resulted of neoplastic nature also at histological inspection. Thus, the overall chemopreventive effect of Avemar (see also Table 1) was nearly 70%, as one obtains from the simple calculus:

$$1 - \frac{0.45 \times 1.3}{0.83 \times 2.3} \approx 0.69 = 69\%$$

The numbers of the aberrant crypt foci (ACF) per area (measured in cm²) was 4.85 in group 2, while in group 3 the number of ACF numbers was 2.03 only (p < 0.0001).

Table 1. Macroscopic findings in the large intestine of F-344 rats treated with Avemar or with Avemar + AOM; statistical significance was: p < 0.001 (*); p < 0.004 (**)

Group	Animals with colon tumors	Average number of colon tumors per animal	Average diameter of the colon tumors	Remarks
1. Untreated controls (n = 10)	0/10	0/10	–	
2. AOM (n = 47)	39/47 (83.0%)	2.3 ± 0.21	2.35 ± 0.25	1 Wilms' tumor
3. Avemar + AOM (n = 29)	13/29 (44.8%)*	1.3 ± 0.17**		2.21 ± 0.12
4. Avemar (n = 9)	0/9	0/9	–	

Modified from (9)

CLINICAL STUDIES: NEW METASTASES AND PROGRESSION-FREE SURVIVAL IN CANCER PATIENTS

An early open-label phase II clinical trial with Avemar was conducted in colorectal cancer patients, involving 30 consecutive subjects undergoing curative surgery, accrued since 1998 up to June 1999 (20). Patients were divided into control cohort (n = 18, 11 men and 7 women with mean age of 70 years) and Avemar cohort (n = 12, 6 men and 6 women with mean age of 64 years) according to their own preference. Patients of the control group received adjuvant chemotherapy alone (if necessary), whereas patients of the Avemar group received adjuvant chemotherapy (if necessary) plus 9 g of Avemar once or twice daily, depending on their body weight. The median follow-up of all patients was 9 months, with range 6-11 months.

At the end of the study, no patients treated with Avemar did show new metastases, neither hepatic, nor in other organs, while 4 patients (22%) did develop new metastases in the control group.

This first clinical result was so encouraging that it was decided to evaluate the impact of Avemar in a second trial involving more patients, and comparing the disease progression-free survival as well as the overall survival in two groups of colorectal patients differing just for the Avemar intake. In the survival analysis trial done with Avemar, as well as in all similar trials, the absolute survival and the disease progression-free survival are normally assessed by a survivor function S(t), defined as

the probability that survival time T is greater than a given time t, e.g., $S(t) = \Pr(T > t)$, and hence

$$S(t) = \int_t^{+\infty} f(u) du = 1 - F(t),$$

where $f(u)$ and $F(t)$ respectively are the probability density and the cumulative probability of T; obviously, the survivor function is very sensitive to the shape of the probability density. In this model, the survivor function must be estimated, assuming that its value is constant between two consecutive events, thus the plot of S(t) versus time is represented by a stepwise decreasing graph.

If all the observed individuals are followed up until the event occurs to each of them, the $\hat{S}(t)$ value, estimating the true S(t), may be evolved from the ratio $\hat{S}(t) = N(T \geq t) / N(0)$, where $N(T \geq t)$ is the number of subjects surviving at time $T \geq t$, and N(0) is the number of subject originally enrolled in the trial. In the case of censored data (like in this second trial), however, this simple calculation cannot be done, and the estimated $\hat{S}(t)$ value must be evaluated by some other methods. One of the most used is the Kaplan-Meier product limit estimator, which is obtained with the formula

$$\hat{S}(t) = \prod_{k|t_k \leq t} \frac{r_k - d_k}{r_k},$$

where r_k is the number of subjects at risk (including censored subjects) at time immediately preceding t_k , and d_k is the number of subjects experiencing the event at time t_k .

Survival analysis allows the assessment of the periods where a given clinical event of interest (death, or any disease progression event like a new metastasis, a relapse, or the death itself) has the highest and the lowest chance. For this purpose, it is used the hazard function h(t) defined by the relationship

$$h(t) = \frac{f(t)}{S(t)} = \frac{d - [\log S(t)]}{d(t)},$$

from which we easily obtain the survivor function in terms of hazard function as follows:

$$S(t) = \exp\left(-\int_0^t h(u) du\right).$$

The survival analysis uses its own regression models. In general, its multiplicative factor must be assumed constant, so that the hazards in the studied cohorts must be proportional. In this case, one is dealing with proportional hazards regression, with hazard ratio constant over time, and different individuals have proportional hazards, so that, if the covariate row vector of subject A is, say, $\mathbf{x}_A = (x_{A1}, x_{A2}, \dots, x_{An})$, and the covariate row vector of subject B is $\mathbf{x}_B = (x_{B1}, x_{B2}, \dots, x_{Bn})$, then the ratio $h(t | \mathbf{x}_A) / h(t | \mathbf{x}_B)$ must not change with time along all the study period. Under this assumption (to be verified at time of data analysis), the hazard function could be written as $h(t | \mathbf{x}) = h_0(t)\xi(\mathbf{x})$, where $h_0(t)$ is the baseline hazard and $\mathbf{X}(\mathbf{x})$

is a relative risk function of the vector of covariates alone. Thus, since the hazard ratio between individuals A and B must be kept constant, one infers that:

$$\frac{h(t | \mathbf{x}_A)}{h(t | \mathbf{x}_B)} = \frac{h_0(t)\xi(\mathbf{x}_A)}{h_0(t)\xi(\mathbf{x}_B)} = \frac{\xi(\mathbf{x}_A)}{\xi(\mathbf{x}_B)}$$

In the case of exponential relative risk, the effect on a log-linear scale is additive, and the baseline hazard function is multiplied by the covariate vector: for this reason, each individual accrued in the trial shows an hazard function of the form:

$$h(t | \mathbf{x}) = h_0(t) e^{\beta' \mathbf{x}}$$

If one models parametrically only the relative risk, as proposed by Cox (21-22), then the shape of baseline hazard may be left unspecified, and a semiparametric model can be constructed, allowing to estimate β from a partial likelihood function which takes into account ties among survival times and does not depend on the hazard function:

$$L(\beta) = \prod_{k=1}^z \frac{\exp(\beta' s_k)}{\left(\sum_{j \in R_k} \exp(\beta' x_j) \right)^{m_k}}$$

where s is the vector sum of the covariates of the m_k individuals surviving for a time t_k .

To analyse the influence of Avemar (added to surgery and standard radiotherapy and/or chemotherapy) on the disease progression-free survival (disease progression events were defined as deaths, relapses and new metastases occurring in both cohorts) and on overall survival (deaths only) in colorectal cancer patients, an open-label comparative cohort trial has been conducted.

For the analysis of the effects exerted by different variables (disease staging, Avemar administration, age, sex, chemotherapy, radiotherapy) on survival, the Cox regression (proportional hazards model) was used, after verifying that this method was suitable according to the study data, by means of the Schoenfeld residuals (23) of the general form:

$$r_{ij} = x_{uj} - \frac{\sum_{k \in R_j} x_{uk} \exp(\mathbf{x}_k \beta_x)}{\sum_{k \in R_j} \exp(\mathbf{x}_k \beta_x)}$$

for each covariate x_u , such that r_{ij} is the existing difference between the covariate value for any failed j -th observation and the average value of the covariate, which is weighted on the basis of estimated hazards from Cox model. The residual analysis for this trial has shown no evidence of violations of the assumptions at the basis of Cox proportional hazards model.

The goal was to determine if the use of Avemar adds any therapeutic benefit compared to standard therapeutical protocols

alone, and therefore, to obtain information on the feasibility of long term administration of Avemar as well as to estimate the expected difference of treatment outcome between cohorts of colorectal cancer patients receiving standard treatment and standard treatment plus Avemar supplementation. For the trials, the chosen values for sample size calculus were $\beta = 0.05$ (i.e., 5%) and $1-\beta = 0.9$ (i.e., the power was 90%), so that a minimal sample size of 50 patients was needed for each cohort.

Beyond the standard oncological treatment used in both groups, the patients assigned to the Avemar cohort did take 9 grammes of Avemar per os once or twice daily, along all the study period, for which the minimal follow-up was at least 6 months. The treatment time period was measured as the interval between the time 0 (baseline) and the last completed visit. Patients of the control cohort received the standard oncological treatment alone, consisting of 5-fluorouracil (5-FU) based chemotherapy and/or radiation therapy, following surgery. All patients were evaluated at baseline, after one month, and then every 12 weeks. Evaluation included imaging quantification of all measurable lesions (by usual radiographic, ultrasonic, or magnetic resonance techniques), laboratory tests (hematology, chemistry, and urinalysis), physical examination, as well as data regarding treatment compliance and toxicity. Tumor progression was defined as an increase of at least 25 percent in the overall tumor size or the appearance of any new lesions; deaths were also recorded. All the time-related events were measured from the date of first diagnosis.

The primary end-point of this study was to compare progression-free survivals of the two cohorts. For this purpose, it was used the two-tailed, unstratified log-rank tests (Kaplan-Meier method), while for other comparisons, z-test, Mann-Whitney's test, Fisher's exact test and Student's t-test were applied as suitable.

The multicenter trial started in November 1998 and patient recruitment lasted up to March 2001, so that 170 consecutive colorectal cancer subjects entered the study (24), to be included in the Avemar or in the control cohorts according to the patient's own decision. The patients had either new diagnosis of their cancer or arrived for routine check-up of their previously diagnosed and treated disease.

The age of the patients of the control cohort was significantly higher than that of the Avemar one (mean was 66.1 years in the controls versus 61.7 years in the Avemar cohort; $p < 0.01$). In contrary, the Avemar patients had significantly more advanced disease stages (Mann-Whitney probe: $z = 4.618$; $p < 0.001$), since 27.3 per cent of the Avemar patients were at UICC stage IV (metastatic), while this value for the control patients was 3.8 % only ($p < 0.001$); moreover, the average time from diagnosis to the study enrolment was significantly longer for the Avemar cohort (11.2 months and 1.1 months, respectively, $p < 0.001$). There were no significant differences between the

average length of time from diagnosis to the last visit (29.6 months and 34.0 months, respectively; Student's $t = 1.494$; $p = 0.137$), nor significant difference between the number of patients receiving chemotherapy ($z = 1.819$; $p = 0.069$), while the controls did receive significantly more radiotherapy ($z = 3.406$; $p < 0.001$). Generally, the prognoses of the Avemar patients at baseline were poorer than those of the control patients.

Table 2. Occurrence of progression-related events

	Avemar (n = 66)	Controls (n = 104)
% patients with new relapses*	3.0	17.3
% patients with new metastases*	7.6	23.1
% deaths**	12.1	31.7
% patients with disease progression events**	16.7	42.3

* $p < 0.01$ ** $p < 0.001$

At end-point analysis, observed progression-related events (relapsed tumors, new metastatic lesions, deaths) were significantly more abundant in the control cohort (Table 2). The log-rank test showed significant differences in favor of the Avemar patients, in both the cumulative probabilities of disease progression-free survival (primary endpoint) and overall survivals. Among all analysed covariates (age, sex, UICC staging, Avemar treatment, radiotherapy and chemotherapy), the only strong predictors of survival in the Cox proportional hazards model were UICC stage and Avemar treatment (Table 3).

Table 3. Multivariate analysis of survival of colorectal patients (Cox regression), proportional hazards model: $\chi^2 = 22.756$; $p = 0.0009$. Among all the six tested variables, only the strong predictors (with significant p value) are shown.

Variable	béta	S.e.m.	Significance	Exp(béta)	95% CI
UICC staging	0.704	0.197	$p = 0.0004$	2.02	1.37-2.98
Avemar treatment	-1.103	0.388	$p = 0.0045$	0.33	0.16-0.71

The treatment with Avemar was generally safe (no serious adverse events were recorded), and the compliance to protocol was good: practically, the only complaint reported by Avemar patients was its disagreeable taste.

The results generally showed highly significant data in favor of Avemar treatment: that was somewhat surprising but not entirely unexpected; rather, the main results confirmed what previously seen in the phase II trial (20). It could be concluded that the present study brought the first evidences that this wheat extract, in combination with surgery plus standard radio/chemotherapy, can significantly inhibit overall tumor progression including the formation of new metastases, and could prolong the survival of colorectal cancer patients. The Cox analysis identified UICC staging and the Avemar treatment (for more than 6 months) as independent survival pre-

dictors. Interestingly, similarly to the previously observed nearly 70% preventing effect exerted by Avemar in rat colon carcinogenesis model (9), in this last clinical trial Avemar increased the probability of survival still by nearly seventy percent (see the $\exp(\beta)$ value in Table 3), since one obtains $1 - 0.33 = 67\%$.

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