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ORIGINAL

A multicentric prospective open trial on the quality of life and oxidative stress in patients affected by advanced head and neck cancer treated with a new benzoquinone-rich product derived from fermented wheat germ (Avemar)

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Abstract
Background and aim Anorexia/cachexia syndrome is frequently correlated with increased oxidative stress (OS). A fermented wheat-germ extract with a standardized benzoquinone content (brand name Avemar) has been shown to exert an intense antioxidant activity with no side effects. The aim of this study was to investigate the effects of Avemar in patients affected by head and neck cancer, correlating the variations with OS with the quality of life as assessed by the Spitzer's index.
Patients and methods A cohort of 60 patients affected by head and neck tumours (stage IIIa, IIIb, IV) were enrolled in the study following an open-label protocol. The patients were assigned to two subgroups, A or B. Group A was treated with conventional oncological therapy alone, and group B was treated with Avemar in addition to standard therapy. After 2 months only 55 patients survived and could be evaluated (29 in the control group and 26 in the Avemar group). Each patient was checked for circulating concentrations of hydroperoxides using the FRAS III test.
Results The levels of OS significantly decreased after 2 months in the group receiving Avemar (group). The value of Spitzer's index was significantly higher in group B, attesting to an improved quality of life.
Conclusion Although the specific active substance in Avemar has not yet been identified, the reduction in free oxygen radicals induced by it is correlated with a clinically significant improvement in the quality of life in patients with advanced cancer.

Keywords Fermented wheat germ extract · Head and neck cancer · Quality of life · Oxidative stress · D-ROMs test

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Introduction

Among cancer patients overall, the characteristic clinical picture of anorexia, reduced food intake, weight loss, wasting of both muscle mass and adipose tissue that often precedes death has been named cancer-related anorexia/cachexia syndrome (CACS) [1–4]. Cachexia itself is even the main cause of death in more than 20% of cancer patients [5]. Besides reduced food intake, CACS is due to metabolic abnormalities, with changes not only in energy metabolism, but also in carbohydrate,

protein, and lipid biochemistry, and changes in the production by the host immune system of proinflammatory cytokines and circulating tumour-derived catabolic factors, and to increased oxidative stress (OS) [6].

Several cytokines, including IL-1, IL-6, TNF-α, INF-α and INF-γ, are involved in the pathogenesis of CACS [7, 8]. The excessive production of proinflammatory cytokines has been implicated, in turn, in the increased OS characteristically found in cancer patients. Increased OS is often marked by an accumulation of free radicals known as reactive oxygen species, such as hydroxyl radicals, superoxide radicals, hydrogen peroxide, and reactive nitrogen species, such as nitric oxide.

Recent studies suggest that the association of a chronic inflammatory condition, typical of patients with advanced cancer, with increased OS adversely affects the immune functions [9, 10]. Moreover, besides the abnormalities induced by the tumour itself, a further mechanism causing increased OS is attributable to the use of antineoplastic drugs, particularly alkylating agents and cisplatin, and of radiation therapy [11, 12]. Indeed, both chemotherapy and radiation therapy are associated with increased production of reactive oxygen species and depletion of critical plasma and tissue antioxidants [6].

An intense antioxidant activity has been shown to be exerted by a fermented wheat-germ extract with a standardized benzoquinone content (code name MSC; brand name Avemar) [14, 15]. This product contains large amounts of chinolonics and flavonoids responsible for an immunomodulatory therapeutic effect, with inhibition of IL-4 and IL-10 production. Moreover, Avemar has recently been shown to induce apoptosis, to inhibit carbon flow to nucleic acid synthesis and to induce the downregulation of major histocompatibility complex (MHC) class I proteins in tumour cells [15–17]. No side effects have been reported with the use of Avemar, which can be considered a medical nutrient [15]. Because of its efficacy and safety, Avemar may play a pivotal supportive role in the treatment of cancer with regard to not only tumour progression, but also attenuating the condition of cachexia associated with terminal malignancy to improve the quality of life (QOL).

In fact, cancer and its associated treatment regimens very often result in global disruption of various aspects of QOL, including physical, functional, psychological, and social well-being [18]. Indeed, besides abnormalities in swallowing, chewing and speaking, the treatment can result in permanent disfigurement [19–21].

In all such patients, the use of Avemar could represent a helpful tool to improve the overall nutritional parameters and therefore QOL. The aim of this study was to verify the effects of the administration of Avemar in a population of patients affected by head and neck cancer, especially in terms of the impact of the use of the product on the multidimensional aspects of their QOL, as assessed according to Spitzer's index, and on OS.

Patients and methods

A group of 60 patients aged 18–65 years affected by head and neck tumours (stage IIIa, IIIb, IV) were enrolled in the study and divided into two subgroups: group A (control group) or group B. Group A received conventional oncological treatment alone, and group B (Avemar group) were treated with the combination of Avemar and standard antitumoral therapy. All the patients were either able to spontaneously eat or receive enteral nutrition and had life expectancies of at least 3 months. All types of medical, radiochemotherapy and/or surgical treatment of the tumoral illness were maintained in all patients during administration of Avemar. All patients taking part in the study gave written informed consent.

The study was conducted following an open-label protocol and included a medical physical examination of the patient at baseline and after 60 days, during which a sample of blood was drawn for routine laboratory tests. For each patient and at each protocol time point the following parameters were recorded: body weight, height, body mass index (BMI), thickness in millimetres of the triceps skinfold, and circulating hydroperoxides (FRAS III test) [22]. This last technique involves the photogenic reaction between free radicals in the blood and a chromogenic substance, developing a molecular complex with a maximum peak of absorbance at 505 nm directly correlated with the concentration of the radicals [22]. Moreover, at each study time point patients filled in the Spitzer's questionnaire for the evaluation of their QOL [23–25]. The questionnaire includes: activity, daily living, health, support, and outlook. Each field includes three possible statements with scores of 0, 1 or 2, meaning a negative, neutral or positive indications, respectively. The patient must choose the statement that best fits his or her own condition, and the higher the total score, which can range from 0 (minimum) to 10 (maximum), the better the QOL. All patients completed the self-administered QOL questionnaire at the hospital with the help of physicians, once at baseline and again after 2 months.

Statistical analysis was performed using Pearson's test with Yates' correction for continuity, Student's *t*-test and the Mann-Whitney *U*-test, after checking for the normality of the distributions (by means of the Shapiro-Wilk or Kolmogorov-Smirnov test) and verifying variance homogeneity (by the Levene test).

The treatment with Avemar consisted of oral administration of 9 g once a day (or twice a day for patients weighing more than 80 kg), either on an empty stomach

or during meals, provided the ingestion of the compound took place at least 2 hours before or at least 2 hours after the intake of products or food containing vitamin C. No negative interactions or undesirable side effects of Avemar in combination with conventional chemotherapy have been described [15].

Results

Of the 60 patients, 55 were still alive after 2 months (29 in group A and 26 in group B). Overall, the treatment was well tolerated by the patients. No patient was withdrawn from the study due to toxicity or significant side effects.

Clinical variables

Both at baseline and after 2 months the control group (group A) showed higher values of BMI than the group receiving Avemar (group B), although group A showed a significant decrease in BMI after 2 months, while group B did not (Table 1).

Spitzer QOL index

At baseline the value of the Spitzer QOL index was higher in group B, without reaching statistical significance, while after 2 months the value of the index was significantly higher in group B (Table 2).

FRAS III test

Circulating hydroperoxides were significantly reduced after 2 months in group B, while they did not show a decrease in the control group A (Table 3).

Table 1 Clinical variables

Variable	Group A (controls)	Group B (Avemar)
Sex (M/F)	14/15	11/15
Age (years)	60.3 ± 4.9	62.3 ± 7.2
BMI (kg/m^2)		
Baseline	22.12 ± 2.90	20.60 ± 3.61
2 months	21.23 ± 2.31	20.88 ± 4.11

Table 2 Spitzer QOL indexes

	Group A (controls)	Group B (Avemar)	p value[a]
Baseline	8 (1–10)	8 (4–10)	0.9589
2 months	8 (4–10)	8 (6–10)	0.0444

[a] Mann-Whitney U-test

Table 3 FRAS III test results expressed in Carr units

	Baseline	2 months	p value
Group A (controls)	423.8 ± 65.9	413.8 ± 65.8	0.1558
Group B (Avemar)	477.1 ± 135.0	436.6 ± 134.9	0.0381

Table 4 Treatment

	Group A (controls)	Group B (Avemar)	p value[a]
Chemotherapy (yes/no)			
Baseline	15/14	11/15	0.6830
2 months	12/17	10/16	0.8748
Radiotherapy (yes/no)			
Baseline	15/14	11/15	0.6830
2 months	11/18	9/17	0.9407
Enteral nutrition (yes/no)			
Baseline	14/15	16/10	0.8963
2 months	18/11	19/7	0.9526

[a] Pearson's test with Yates' correction for continuity

Treatment

At baseline, 15 patients in group A and 11 patients in group B were undergoing treatment with chemotherapy, 15 in group A and 11 in group B were undergoing treatment with radiotherapy, and 14 in group A and 16 in group B were receiving enteral nutrition. After 2 months, 12 patients in group A and 10 patients in group B were undergoing treatment with chemotherapy, 11 in group A and 9 in group B were undergoing treatment with radiotherapy, and 18 in group A and 19 in group B were receiving enteral nutrition (Table 4).

Laboratory tests

The results of the laboratory tests (Table 5) confirmed that the use of Avemar was safe and caused no alteration in renal and/or hepatic function. Both the groups were malnourished according to serum cholesterol and transferrin values at baseline (cholesterol 172.4 ± 65.2 mg/dl in group A and 184.5 ± 56.4 mg/dl in group B; transferrin 224.3 ± 54.2 ng/ml in group A and 220.4 ± 74.3 ng/ml in group B). After 2 months these nutritional indexes showed a nonsignificant trend to improvement (cholesterol 183.0 ± 41.7 mg/dl in group A and 195.8 ± 36.5 mg/dl in group B; transferrin 235.6 ± 63.1 ng/ml in group A and 245.3 ± 67.0 ng/ml in group B)

With regard to blood cells (Table 6), group B (Avemar) showed a significantly higher level of WBCs at baseline, while the number of RBCs was higher in the control group A after 2 months.

Table 5 Laboratory test results

	Group A (controls)	Group B (Avemar)	*p* value
Glucose (mg/dl)			
Baseline	86.42 ± 8.99	92.50 ± 13.36	0.0486[a]
2 months	92.42 ± 11.49	96.58 ± 16.49	0.2905[a]
Creatinine (mg/dl)			
Baseline	0.66 ± 0.13	0.51 ± 0.13	0.3412[a]
2 months	0.67 ± 0.16	0.59 ± 0.13	0.2954[a]
Triglycerides			
Baseline	107.15 ± 41.09	120.19 ± 36.87	0.2426[a]
2 months	54 ± 47.98	120 ± 31.24	0.0879[b]
ALT (U/l)			
Baseline	20.73 ± 7.63	25.41 ± 8.65	0.0393[a]
2 months	23.11 ± 7.11	26.56 ± 7.52	0.1272[a]
AST (U/l)			
Baseline	17.61 ± 6.37	23.91 ± 10.05	0.0062[a]
2 months	25.22 ± 9.70	24.39 ± 9.20	0.7746[a]
γGT (U/l)			
Baseline	23 ± 42.4	24 ± 52.2	0.4652[b]
2 months	25 ± 54.5	29 ± 48.5	0.3415[b]
Cholesterol (mg/dl)			
Baseline	172.4 ± 65.2	184.5 ± 56.4	0.3446[b]
2 months	183.0 ± 41.7	195.8 ± 36.5	0.2962[a]
Baseline *vs* 2 months		0.0835[a]	0.0954[a]
Transferrin (ng/ml)			
Baseline	224.3 ± 54.2	220.4 ± 74.3	0.8577[b]
2 months	235.6 ± 63.1	245.3 ± 67.0	0.6839[a]
Baseline *vs* 2 months		0.1968[a]	0.0876[a]

[a] Student's *t*-test, [b] Mann-Whitney *U*-test

Table 6 Blood cells

	Group A (controls)	Group B (Avemar)	*p* value
WBC (x10^3/mm^3)			
Baseline	3.89 (3.82–6.34)	5.78 (2.82–10.40)	0.0005[b]
2 months	4.39 (2.98–42.0)	4.29 (2.66–9.50)	0.8771[b]
RBC (x10^6/mm^3)			
Baseline	4.23 (2.56–5.00)	4.00 (3.09–4.96)	0.9043[b]
2 months	4.35 (3.99–5.42)	4.10 (2.50–6.37)	0.0046[b]
Haemoglobin (g/dl)			
Baseline	12.7 (7.9–14.5)	12.6 (9.9–15.0)	0.8166[b]
2 months	13.1 (8.9–15.8)	12.1 (9.2–13.9)	0.0599[b]
Haematocrit (%)			
Baseline	37.6 (24.9–48.0)	39.6 (29.0–46.0)	0.2462[b]
2 months	38.9 (27.8–45.2)	40.0 (32.0–44.0)	0.7494[b]
MCV (fl)			
Baseline	94.8 ± 8.9	93.9 ± 7.2	0.7295[a]
2 months	93.1 ± 7.3	92.2 ± 10.3	0.7124[a]
MCH (pg)			
Baseline	31.1 ± 3.3	30.1 ± 4.0	0.3664[a]
2 months	31.2 (25.0–33.9)	27.8 (21.1–40.0)	0.0186[b]
Lymphocytes (x10^6/l)			
Baseline	957 (200–2,900)	1170 (310–3,000)	0.5591[b]
2 months	1100 (580–2,000)	1115 (620–2,500)	0.6366[b]

[a] Student's *t*-test, [b] Mann-Whitney *U*-test

Signs and symptoms

The signs and symptoms that correlate with the pathology and/or with antineoplastic therapies were evaluated on a scale ranging from 0 to 4 (Table 7). The evaluation was done by different assessors. Thus the *p* values (where analysis was possible) do not have strong inferential properties, and may describe the state of the studied sample, but not the effect on the whole population from which that sample was drawn.

Table 7 Signs and symptoms

	Group A (controls)	Group B (Avemar)	*p* value[a]
Dysphagia			
Baseline	2 (0–4)	3 (0–4)	0.4866
2 months	3 (0–4)	3 (0–4)	0.9863
Vomiting			
Baseline	0 (0–4)	0 (0–1)	0.0991
2 months	0 (0–4)	0 (0–2)	0.1693
Nausea			
Baseline	1 (0–4)	0 (0–2)	0.0097
2 months	0 (0–4)	0 (0–2)	0.1284
Diarrhoea			
Baseline	0 (0–4)	0 (0–1)	0.0599
2 months	1 (0–4)	0 (0–0)	0.0013
Stipsis			
Baseline	1 (0.4)	0 (0–3)	0.0213
2 months	0 (0–4)	0 (0–3)	0.1241
Tolerability			
Baseline	4 (4–4)	2 (0–4)	0.0001
2 months	No data	2 (1–4)	Not evaluable

[a] Mann-Whitney *U*-test

Discussion

Avemar is a dietary supplement that can be used as a supportive therapy in human cancer to reduce the incidence of metastasis and disease progression, and to improve CACS and survival rate [15, 26, 27].

In our open-label study we examined the effects of the administration of Avemar over a period of 2 months in a group of 22 patients affected by head and neck tumours (stage IIIa, IIIb, IV) receiving conventional chemo- and/or radiotherapy, while a control group of 33 patients with comparable pathology received only conventional antitumoral therapy. In particular, we evaluated the influence of Avemar on QOL, assessed according to Spitzer's index, in relation to variations in the mediators of OS (free oxygen radicals) as detected by the FRAS III test. In fact, a clinically significant OS occurs in patients with advanced cancer [28, 29], and together with CACS, is highly predictive of clinical outcome and survival, besides a more general feeling of well-being. Although the changes in QOL and oxidative status that we observed were related to a relatively short time period, the signs and symptoms of the disease displayed significant variations in terms of the Spitzer's index and FRAS III test.

Besides the presently available oncological treatments, complementary nutritional support with supplements with antioxidant properties, such as vitamins A, C and E, α-lipoic acid, *N*-acetyl cysteine, in combination have been shown to be effective in ameliorating CACS through improved appetite, increased food intake and weight gain, and reduced resting energy expenditure and OS [30].

In this study, we confirmed that treatment with Avemar as an adjuvant to standard oncological therapy results in a greater subjective improvement in well-being than conventional antitumoral therapies alone can achieve in patients with head and neck cancer. The positive influence on mood could act through the free radical scavenging effect of components of Avemar and particularly through their inhibition of proinflammatory cytokines, which have been shown to induce alterations in brain function analogous to the behavioural and biological abnormalities occurring in depressed patients [31].

No toxic side effects or disadvantageous interactions with the cytostatic drugs used were recorded.

Supportive use of Avemar may thus improve the patient's performance status and enhance the antitumoral effects of standard therapies. In fact, because of the very short survival of these patients at this stage of the disease, symptomatic advantages in terms of QOL rather than just nutritional aspects should be underlined. Indeed, the results of this study show that administration of Avemar improves QOL and alleviates fatigue even at the relatively short end-point of two months.

The biochemical explanation of the effects of Avemar includes protection from OS and modulation of proinflammatory cytokines and enzymes, such as inhibition of ribonucleotide reductase, which is responsible for the conversion of ribonucleotides to the precursors of DNA synthesis deoxyribonucleoside triphosphates, and reduction of cyclooxygenase-1 and -2 activity, which are responsible for the production of inflammation mediators [16, 26]. Moreover, early biochemical events, such as inhibition of tyrosine phosphatase activity and elevation of intracellular Ca^{2+} influx, induce a significant downregulation of the MHC class I molecules on the surface of the tumour cells, thereby exposing them to the action of natural killer cells [32]. On the other hand, macrophages exposed to Avemar show upregulation of the secretion of TNF-α, resulting in increased antitumour activity of these cells [15].

Besides, it has been shown that Avemar is capable of inducing the expression of intercellular adhesion molecule-1 (ICAM-1) on endothelial cells, thereby allowing the development of an effective leucocyte infiltrate of the tumour, an effect that is impaired in human malignancies because of the reduced levels of ICAM-1 in the vasculature of tumoral tissue [33].

However, the specific active substance of Avemar has not yet been identified, and it is not possible, at the moment, to fully elucidate the observed biochemical effects. Thus, a better understanding of the responsible molecule or compound will lead to further development and application of Avemar as a chemopreventive and anticancer drug.

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