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Apparent Partial Remission of Breast Cancer in 'High Risk' Patients Supplemented with Nutritional Antioxidants, Essential Fatty Acids and Coenzyme Q_{10}

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Abstract—Thirty-two typical patients with breast cancer, aged 32–81 years and classified 'high risk' because of tumor spread to the lymph nodes in the axilla, were studied for 18 months following an Adjuvant Nutritional Intervention in Cancer protocol (ANICA protocol). The nutritional protocol was added to the surgical and therapeutic treatment of breast cancer, as required by regulations in Denmark. The added treatment was a combination of nutritional antioxidants (Vitamin C: 2850 mg, Vitamin E: 2500 iu, β-carotene 32.5 iu, selenium 387 μg plus secondary vitamins and minerals), essential fatty acids (1.2 g gamma linolenic acid and 3.5 g n-3 fatty acids) and Coenzyme Q_{10} (90 mg per day). The ANICA protocol is based on the concept of testing the synergistic effect of those categories of nutritional supplements, including vitamin Q_{10}, previously having shown deficiency and/or therapeutic value as single elements in diverse forms of cancer, as cancer may be synergistically related to diverse biochemical dysfunctions and vitamin deficiencies. Biochemical markers, clinical condition, tumor spread, quality of life parameters and survival were followed during the trial. Compliance was excellent. The main observations were: (1) none of the patients died during the study period. (the expected number was four.) (2) none of the patients showed signs of further distant metastases. (3) quality of life was improved (no weight loss, reduced use of pain killers). (4) six patients showed apparent partial remission.

Introduction

The National Research Council (1982) published a scientific survey of the relationship of diet and nutrition to cancer. In the United States, about 20 per cent of deaths are caused by cancer. One conclusion was that differences in the rates of occurrence of various cancers in different human populations are frequently correlated with differences in diets. Scientific and medical research on the role of antioxidants and nutritional factors

in the genesis and prevention of cancer is increasingly acknowledged and studied. Breast cancer causes more deaths among women aged 40–44 than any other disease. It is known to be associated with hormonal activities, and diet was believed to have a major role as early as 1973. Vitamins and cancer prevention have been detailed (Greenwald, 1991).

Folkers *et al.* (1982) recorded the immunological significance of an increase in levels of IgG in the serum of patients treated with vitamin Q_{10}. Three patients with cancer, four with cardiovascular disease, and one with diabetes mellitus responded positively during 28–97 days. Retrospectively, the dosage of 60 mg of vitamin Q_{10} daily is believed to have been too low. It was understood that the timing of clinical responses probably reflected the transcriptional increase in mRNA and a translational increase in the level of apoenzymes for vitamin Q_{10}, based on mechanisms reviewed by Walker (1977). Sugimura *et al.* (1977), Azuma *et al.* (1978), and Niotani *et al.* (1979) recorded research on vitamin Q_{10} and immune mechanisms. Further, vitamin Q_{10} is shown to be efficient in counteracting the side-effects of anthracycline and even making higher dosages of chemotherapeutic agents possible (Mortensen *et al.*, 1986).

Folkers *et al.* (1991) recorded greater deficiencies of vitamin Q_{10} in the blood of cancer patients than in the blood of control subjects. They considered that an impaired biosynthesis of vitamin Q_{10} can occur in cancer patients because of nutritional deficiencies, especially in view of the multiple vitamin requirements for the biosynthesis of vitamin Q_{10} from phenylalanine in the human body.

Folkers *et al.* (1994) published a critique of 30 years of research on the hematopoietic and immunological activities of vitamin Q_{10}, and the potentiality of a therapy for cancer. Vitamin Q_{10} has been found to stimulate the host defense system for resistance to bacterial, viral and protozoal infections and to senescence, and to chemically-induced neoplasia. The data of this critique were considered to support rationales for trials of immunotherapy of cancer with vitamin Q_{10}.

Folkers *et al.* (1993b,c) recorded blood levels of vitamin Q_{10} in cancer patients in America and in Sweden, and summarized (Folkers *et al.*, 1993a) the information on the survival of 10 cancer patients treated with vitamin Q_{10}. The vitamin caused no significant side-effects, and was associated with survival for periods of 5–15 years. The justification of new systematic protocols was emphasized.

Ames (1983) reviewed dietary anticarcinogens. Birt (1989) reviewed the effects of the intake of selected vitamins and minerals on cancer prevention. Watson (1986) reviewed the immunological enhancement by fat-soluble vitamins, minerals and trace elements. Batist (1988) reviewed selenium and preclinical studies of its anticancer therapeutic potential. Nair and Schwartz (1990) reviewed the immunoregulation of natural and lymphokine-activated killer cells by selenium.

Muto and Moriwaki (1984) reviewed the antitumor activity of vitamin A and its derivatives. Temple and Basu (1988) critically appraised the use of beta-carotene to prevent cancer. Begin *et al.* (1985) reviewed the selective killing of human cancer cells by polyunsaturated fatty acids. Van der Merwe *et al.* (1987) reported marked subjective improvement in most of 21 patients with untreatable malignancy when supplemented

with gamma-linolenic acid. The clinical application of anti-oxidants has been reviewed by Noto *et al.* (1989) and by Floyd (1990).

Kneckt *et al.* (1990) found in an epidemiological study an 11 times higher risk of breast cancer with low selenium and vitamin E in conjunction. Preliminary results from intervention studies seem to yield similar findings (Blot *et al.*, 1993; Adjuvant Nutrition in Cancer Treatment (Symposium, 1992).

These studies on vitamins and nutritional entities and their relationship to the prevention and treatment of cancer were some of more than 200 references forming the basis for our protocol on the treatment of breast cancer with nutritional entities, and particularly vitamin Q_{10}.

Design of Clinical Trial

Thirty-two women with breast cancer in the so-called high risk group were included in an open and still ongoing trial, for which they gave their informed consent.

This report is based on an 18 months follow-up study. For ethical reasons, and anticipating lack of compliance with the large number of supplements, the trial was open and aimed towards a finding of a possible positive response, which would then be a basis for a blinded trial.

All patients were treated according to the routine procedure in Denmark, i.e. surgery, chemotherapy, X-ray treatment and in some cases Tamoxifen in accordance with the estrogen receptor status of the tumor.

The patients were between 32 and 81 years. Beside the spreading of cancer to the lymph nodes, some of the patients had metastases at different sites such as the skin, the pleura or in the thoracic vertebrae.

All patients underwent clinical check-ups every 3 months in order to detect any recurrence of the disease. Mammography, bone scan and X-ray pictures of the chest or spine were performed whenever there was any suspicion of recurrence. Open biopsies or 'Trucut (R)' biopsies were also performed. Blood pressure, body weight, use of painkillers and quality of life parameters were followed.

At 0, 3 and 12 months, blood tests of Coenzyme Q_{10} (whole blood) were obtained, in order to follow compliance. For a random subgroup of 1/3, extensive hematological, immunological and nutritional parameters were followed including whole blood Q_{10}, whole blood calcium, magnesium, selenium, manganese, zinc, copper, lithium and serum Vitamin E, B6 and β-carotene. Furthermore, blood cell counts were performed.

Substances used in the intervention trial

All patients took the following supplements in a daily pack divided morning and evening (Table 1.)

Table 1. Bio-antioxidant contains all the basic antioxidants. The amounts stated below under "total dose" are the combined doses received from 3 Bio-antioxidants plus the relevant "mono" preparations. The tablets/capsules were supplied by Pharma Nord, Denmark

Preparation	No. of tablets	Total dose
Bio-Quinone Q10	3	90 mg Coenzyme Q_{10}
Bio-Glandin	10	1.2 g GLA (n-6)
Bio-Marine	10	3.5 g n-3 FA
Bio-Vitamin C, 750mg	3	2850 mg Vitamin C
Bio-Vitamin E, 350mg	4	2500 iu Vitamin E
Bio-Carotene, 9mg	4	32500 iu β-carotene
Bio-Selenium, 100 μg	2	387 μg Selenium
Bio-Antioxidant	3	2500 iu Vitamin A
		15 mg Vitamin B1
		15 mg Vitamin B2
		75 mg Vitamin B6
		13 μg Vitamin B12
		45 mg Niacin
		22 mg Pantothenic
		300 μg Folic Acid
		300 μg Biotin
		300 iu Vitamin D
		150 mg Magnesium
		22 mg Zinc
		3 mg Copper
		6 mg Manganese

Data on biochemical markers.

Table 2 shows the levels of CoQ_{10}, vitamins and minerals together with an analysis of statistically significant differences between onset and 12 months (Wilcoxon's test). Only data where all three measurements have been obtained are included. Except for Q_{10}, examined in 27 patients, on average all data are available in 10 patients.

Baseline data for NK-cells and lymphocytes are missing; therefore statistical difference is calculated between the 3 and 12-month data.

Discussion on biochemical markers

The increase in the vitamin and selenium content is a reflection of patients' compliance, and the levels reached are within the expected range from supplementation in dosages

Table 2. Biochemical Markers

	Zero	3 months	12 months	Significance level
Coenzyme Q10 (mg/l)	0.82	1.45	1.60	$p<0.01$
Beta-carotene (μg/l)	838	3451	2862	$p<0.01$
Vitamin E (mg/l)	11.3	35.2	33.4	$p<0.05$
Vitamin B6 (μg/l)	30	625	641	$p<0.01$
Selenium (μg/l)	138	430	547	$p<0.01$
Calcium (mg/l)	61.03	62.83	61.64	N.S.
Magnesium (mg/l)	35.43	32.33	33.38	N.S.
Manganese (μg/l)	9.8	10.1	9.1	N.S.
Zinc (mg/l)	7.51	7.19	7.68	N.S.
Iron (mg/l)	445.6	412.2	429.2	N.S.
Copper (mg/l)	1.23	1.33	1.26	N.S.
Lithium (mg/l)	0.016	0.015	0.015	N.S.
Helper/suppressor cell ratio %	1.20	1.25	1.25	N.S.
Natural Killer cell count	—	207	253	$p<0.05$
Lymphocyte cell count	—	1355	1894	$p<0.05$

as those stated above. Lack of change in a number of blood minerals can be seen as a noninterference for the elements given in zero or moderate dose.

The available control blood levels of CoQ_{10}, before the administration of CoQ_{10}, allow the calculation of a mean value of 0.82 +/−0.30 mg/l (n=27). The mean value for American non-patients (unpublished) was 0.81 +/− 0.2 mg/l (n=49). There is obviously no significant differences between these two mean values.

Our patients were medically advised to take 90 mg of CoQ_{10} daily, and the data show that after 3 months the mean level of CoQ_{10} was 1.45 +/− 0.56 mg/l, which is significantly higher ($P<0.01$) than the mean baseline value. Since people without overt disease generally show a range of 0.5–1.5 mg/l of CoQ_{10}, these data on the mean blood level after 3 months on 90 mg daily are quite close to the range of people not on CoQ_{10} therapy, which indicates that a daily dosage of 90 mg was too low for many of these 27 patients. However, six of the 27 patients showed blood levels above 1.5 mg/l, and up to 2.81 mg/l.

The data on levels of CoQ_{10} in blood after 12 months treatment allow the calculation of a mean blood level of 1.60 +/− 0.62 mg/l (n=19) which is not significantly different from the blood level after 3 months.

The blood levels of CoQ_{10} were significantly higher ($P<0.01$) after periods of 3–12 months in comparison with the control data.

Comparing our patients with expected Q_{10}-increase from the same preparation and dose in normal controls (internal data), the cancer patients showed less increase in Q_{10}-level than the normals, indicating an increased need or less uptake.

Data on CoQ_{10} levels for five of the six patients showing some apparent remission revealed a mean level of 0.64 +/− 0.17 mg/l (n=5). The blood levels after treatment with CoQ_{10} for 3 months for these five patients showed that only two of the five obtained blood levels well above 1.5 mg/l, which again indicates that the daily dosage of CoQ_{10} was too low.

Selected Clinical Data

The following important clinical case histories were accumulated for six of the 32 patients.

Patient E.M.M., 64 years, had verified metastases to the Xth thoracic vertebra. During the intervention trial her dosage of 520 mg of morphine was tapered off and replaced by 1000 mg of aspirine, twice daily. Five to six years previously, she had a double-sided mastectomy. Postoperatively, she had local X-ray treatment and Tamoxifen (30 mg) daily. Objective examinations, i.e. Tc bone scanning and CT scanning revealed no progression in her disease.

Patient E.L., 52 years, had a mastectomy 1 year prior to this trial. She had local recurrence on the chest and in the pleura. This recurrence was verified by chest X-ray and microsopic examination of the pleural fluid, which showed tumor cells. A few weeks before this trial she had been treated with cyclophosphamide fluroblastine. She was in a bad clinical condition, but a few weeks after entry into the trial her condition was significantly improved, and X-ray examination revealed that she no longer had fluid in the pleura or metastases in the lungs.

Patient S.P., 70 years, had a lobular carcinoma shown by biopsy in the right breast, and a mastectomy was recommended. After 6 months, a mastectomy was performed. Subsequent histological examination revealed residual tumor, i.e. resection was incomplete. Subsequently, during this trial, there were no further signs of recurrence and the patient was in an excellent clinical condition. The histology of the tumor bed after mastectomy could no longer demonstrate tumor tissue.

Patient G.C., 82 years, had had a mastectomy 8 years previously. Histology revealed a ductile carcinoma, grade II, with metastases to the axilla, and infiltration of tumor into nerves on both sides of the breast. When she entered this trial, there were numerous metastases on the skin around the scar, and on both the right and left sides. After six clinical examinations during this trial, the metastases on the skin had diminished. Also, the lymph node in the right axilla diminished so it was no longer palpable. The patient was in excellent clinical condition.

Patient B.H., 54 years, had carcinoma of the right breast, and had had a mastectomy. She entered this trial just before starting chemotherapy. She experienced no hair loss, and there was no decrease in the vital values. She was in excellent clinical condition.

Patient I.L.P., 48 years, had had a prior mastectomy performed because of a tumor in the right breast of about 3 cm in diameter. She had positive lymph nodes in the axilla, and received six courses of chemotherapy with CMF. During the trial, she was re-operated because of a small local recurrence in the scar, and had X-ray treatment. In this trial she was in excellent clinical condition without any further distal spread.

Clinical overview of the six patients

The treatment in this trial, in addition to the conventional surgery and therapy of breast cancer medically required in Denmark, resulted in six cases achieving excellent clinical condition. Some remission was apparent, and the patients emphasized that they felt very good.

Clinical overview of all 32 patients

None of the 32 patients died during the 18 months follow up on test treatment. From statistical prognostic data on breast cancer (Dombernowsky *et al.*, 1988) four of our patients would have been expected to have died during the 18 month period.

The patients experienced no weight loss.

The use of pain-killers was reduced.

Quality of life was improved.

None of the patients showed any sign of progression of eventual distant metastases.

None of the patients showed any sign of side-effects, except for a tendency to yellowish palms due to the beta-carotene, and occasional fish oil taste for some patients.

Discussion

The apparent partial remission in six patients as well as the improvement in clinical condition in the remaining 26 patients and the excellent survival rate are encouraging.

The 32 women continue in the trial, and an observation period of at least another 2–3 years will be needed before definite conclusions can be drawn.

However, based on the quality of life parameters, other researchers will be encouraged to initiate trials with the same objectives.

It is our experience that the total number of tablets is only acceptable for participants who are highly motivated. We therefore think that it might be difficult to do the same trial in a double-blind design with the same compliance, due to the high amount of tablet supplementation needed.

From our blood data on Q_{10} compared with the experiences from cardiac patients, we would recommend a higher dose — preferably 300 mg of Coenzyme Q_{10}/day.

The multiplicity of the nutritional entities in our clinical protocol restricts a selection of any specific nutritional entity, including vitamin Q_{10}, as a dominant cause of improvement. The apparent regression of breast cancer in six of the patients, and the improved well-being and possibly survival of the patients, are now justification for further clinical trials emphasizing specific nutritional entities, particularly vitamin Q_{10}.

Status at 24 months

Since this paper was written a further 6 months' collection of data has been possible.

In early 1994 the status of the 32 patients is unchanged and no patient has died. Two patients have verified complete regression related to increased dose of Coenzyme Q_{10} to 300–390 mg/day (Lockwood *et al.*, 1994).

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