The Treatment of Cancer with a Combination of Broad-Spectrum Micronutrients: Review of Six Relevant Studies

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Abstract *Five of six studies to date have documented that standard oncologic care (i.e., some combination of surgery, radiation, chemotherapy, and/or immunotherapy) combined with a broad-spectrum of micronutrients (i.e., some combination of vitamins, minerals, and/or essential fatty acids) normally present in the human body results in increased lifespan and/or improved quality of life among cancer patients who are either terminally ill, end-stage, or high-risk (i.e., having very poor prognoses). The author has summarized these studies and provided clinical recommendations based on the safety and efficacy of this treatment approach.*

Introduction

Published evidence confirms that a combination of antioxidants are more effective against cancer than individual antioxidants.[1-3] Published evidence also confirms that reactive oxygen species can activate all stages of carcinogenesis.[4] This means that a combination of micronutrients possessing anti-oxidative properties should be capable of retarding the cancerous process even when it is readily apparent or in the advanced stages. While there are numerous studies showing that combinations of several antioxidants confer benefits, there is a scarcity of studies using a combination of many micronutrients (i.e., a broad-spectrum) to assuage the progression of cancer. To this author's knowledge, there have only been six such published studies of varying rigor that have evaluated the efficacy of broad-spectrum micronutrients. Five of six studies to date have documented that standard oncologic care (i.e., some combination of surgery, radiation, chemotherapy, and/or immunotherapy) combined with broad-spectrum micronutrients (i.e., some combination of vitamins, minerals, and/or essential fatty acids) normally present in the human body results in increased lifespan and/or improved quality of life among cancer patients. This review will summarize these studies and provide clinical recommendations based on the safety and efficacy of this treatment approach.

Hoffer's Orthomolecular Treatment Program

Dr. Abram Hoffer treated more than 1,000 cancer patients in his very distinguished career.[5] The majority of these cancer patients were in the advanced stages of the disease and were considered terminal when they were evaluated and treated by the combination of orthomolecular substances developed by Hoffer (**Table 1**, p.7). The results of his work with cancer patients was published with coauthor, Dr. Linus Pauling, in several journal publications and in one book.[5-7]

Their first study involved 134 patients registered with Hoffer between August 1977

and March 1988.[6] Thirty-three patients were in the non-random control group (received standard oncologic care involving either surgery and/or radiation with or without chemotherapy) and 101 patients were in the combined treatment group (received a combination of orthomolecular and standard oncologic care). The study was terminated on December 31, 1989. The mean ages of the patients in this study, as derived from four cohorts (two control groups and two treatment groups), were 53.1, 52.8, 51.9, and 55.3 years respectively. The patients in the combined treatment group had an increased life expectancy far above that of the patients in the non-random control group. The mean survival time for the main subgroup (n=31) of non-random controls was 5.7 months, which is comparable to ambulatory patients having reached or almost reached the terminal stage of cancer. The mean survival time of similar patients (n=81) who followed the combined treatment continuously until the study was terminated was 92 months, an effect attributed to the addition of orthomolecular substances to standard oncologic care.

In their second publication, another group of cancer patients who registered at Hoffer's office for care from April 1, 1988 to December 31, 1989 were analyzed.[7] The study involved 170 cancer patients, with 20 in the non-random control group (standard oncologic care) and 150 in the combined treatment group (received a combination of orthomolecular and standard oncologic care). The study was terminated on December 31, 1992. The mean ages of all patients were not provided, but a cursory review shows that the ages are similar to those patients analyzed in Hoffer's first publication. From the 20 cancer patients in the non-random control group, only three (15%) were still alive when the study was terminated. From the treatment group, 52 of 138 patients who followed the combined treatment (38%) remained alive at the termination date. Given the fact that this study was considerably shorter than the first study, the mean survival differences (in months) were not much different between the standard oncologic care group and the combined treatment group **(Table 2**, p.7). However, Hoffer and Pauling do mention that among patients classified as "good" responders in the combined treatment group, they had a mean survival time about four times that of controls. Unfortunately, they did not include the actual data to support this statement within the body of their second publication so it is difficult to verify.

In a further examination of his original cohort of 134 patients, Hoffer found a continuous therapeutic difference between the treatment group and the non-random controls many years after the study was initiated.[8] By January 1, 1992, 41 patients were still alive from the combined treatment group and only one patient was alive from the non-random control group. As of December 31, 1993, 16 years after the study began, 34 (about 34%) of those patients from the combined treatment group were still alive, while all of the patients (0%) that had received standard oncologic care had died. The best results were obtained by combining standard oncologic care and orthomolecular treatments. Hoffer concluded that patients must be on the combined program for a minimum of two months before it can begin to increase survival (extend life).[5-8]

With respect to Hoffer's program, many of his patients were also provided with 10,000-50,000 IU/day of vitamin A, but this vitamin was not part of the original published protocol as described in his reports with Pauling.[6,7] Beginning in 1992, Hoffer recommended that many of his cancer patients add coenzyme Q_{10} to their orthomolecular regimen.[8] The coenzyme Q_{10} apparently augmented the curative properties of the orthomolecular plan. Hoffer recommended an initial daily dose of 300 mg, and when the cancer had achieved remission, the daily dose was then reduced to 100-150 mg.[8]

Jaakkola et al's Micronutrient Approach to Small Cell Lung Cancer

This non-randomized study, published in 1992, involved 18 patients (4 women and 14 men, mean age 60.4 ± 7.8 years) with small-cell lung cancer (SCLC).[9] Patients received

Table 1. Hoffer's "Typical" Orthomolecular Treatment Program for Cancer

Micronutrient	Daily Dosage
Vitamin C	12 g
Vitamin B_3	1.5-3.0 g
Vitamin B_6	250 mg
Folic acid	5-10 mg
Other B-Vitamins	25 to 50 times the RDA
Vitamin E (D-alpha tocopherol)	800 IU
Beta-Carotene	10,000-75,000 IU
Coenzyme Q_{10}	300 mg
Selenium	200-500 mcg
Zinc	50-220 mg
Sometimes calcium, magnesium or a multi-mineral tablet	As determined by the clinician

Table 2. Mean Survival Results for Patients Given Standard Oncologic Care and Combination Treatment (Hoffer's Program plus Standard Oncologic Care)

Treatment	Mean Survival (Months) Involving Original Cohort of 134 Patients (22 Patients Excluded)[1]	Mean Survival (Months) Involving Second Cohort of 170 Patients (67 Patients Excluded)[2]
Standard Oncologic Care	5.7 (n=31)	6.7 (n=17)[3]
Combination Treatment	92 (n=81)	6.2 (n=86)[4]

1. Registered with Hoffer between August 1977 and March 1988; study terminated December 31, 1989 (12-year evaluation period).
2. Registered at Hoffer's office for care from April 1, 1988 to December 31, 1989; study terminated December 31, 1992 (4-year evaluation period).
3. This number was calculated by adding up the total number of days lived until death for all patients, then dividing that total by the number of patients (3,440 total days/17 patients =202.4 days per patient), and then dividing that figure by 30 days per month (202.4/30=6.7 months) to give the average survival (in months) for this group.
4. This number was calculated by adding up the total number of days lived until death for all patients, then dividing that total by the number of patients (15,937 total days/86 patients =185.3 days per patient), and then dividing that figure by 30 days per month (185.3/30=6.2 months) to give the average survival (in months) for this group.

a number of vitamins, essential fatty acids, and trace elements (**Table 3**, p. 8) along with conventional treatment (chemotherapy and/or radiation at regular intervals). Like in the Hoffer and Pauling studies, this cohort was given a combination of daily micronutrients plus standard oncologic care.

The endpoint of the study was the survival time of the patients from the time of diagnosis compared to survival statistics obtained from previous published studies. Jaakkola et al noted that typically 50% of patients

Table 3. Daily Micronutrients Administered to Patients with Small-Cell Lung Cancer

Vitamins and Essential Fatty Acids Daily	Dose Ranges
Vitamin A (retinol palmitate)	15,000-40,000 IU
Beta Carotene	10,000-20,000 IU
Vitamin E (D-alpha tocopherol)	300-800 IU
Vitamin B_1	150-750 mg
Vitamin B_2	15-50 mg
Vitamin B_3 (niacinamide)	150-400 mg
Vitamin B_5 (calcium pantothenate)	50-300 mg
Vitamin B_6	200-1,140 mg
Vitamin B_{12} (cyanocobalamin)	30-1,600 mcg
Vitamin D_3 (cholecalciferol)	400-1,000 IU
Vitamin C	2,000-5,000 mg
Biotin	300-10,000 mcg
Essential Fatty Acids	5-65 g*
Trace Elements (all doses in elemental quantities)	
Calcium	500 mg 1-2/day
Chromium	780 mcg 2-4/day
Copper	3mg/day
Magnesium	250 mg 1-2/day
Manganese	97 mg 1-2/day
Potassium	120 mg/day
Selenium	856 mcg 2-4/day
Vanadium	234 mcg 2-4/day
Wolfram (a.k.a., Tungsten)	1,114 mcg 2-4/day
Zinc	9.1 mg 3-5/day

*The composition of essential fatty acids was not specified.

with SCLC die within six months, and the 2-year survival rate is less than 15%. In their study, patients given combination treatment lived considerably longer with 77% of patients (n=14) surviving longer than 12 months, and the 2-year survival rate was 33% (n=6). The median survival was 505 days for the entire group. One of their patients lived more than five years. Ten patients died and had a mean survival time of 15 ± 8 months, whereas eight patients (44%) remained alive at study termination with a mean survival of 32 months. Six of these eight patients had limited disease before the combined approach was undertaken.

Other noteworthy findings in their study had to do with the patients who remained alive at study termination. They found that these patients had significantly higher baseline (pre-treatment) whole blood zinc levels (p=0.047) compared to those patients who died during the study. They also found that the surviving patients began the nutritional treatments within a mean of 81 days (standard error: 32.5 days) from diagnosis compared to the patients who died who began the nutritional treatments within a mean of 156 days (standard error: 52.8 days) from diagnosis. Clearly, starting the combination treatment earlier conferred a therapeutic benefit since patients who started earlier generally lived longer. Patients with limited

disease at the onset of treatment also fared better. No side effects were reported from the nutritional treatments. Patients on the combined approach appeared to tolerate the chemotherapy and/or radiation better than patients given standard oncologic care only since Jaakkola et al observed that they all received the complete amount of standard oncologic care without having any major haematological problems.

Lamm et al's Micronutrient Treatment Approach to Transitional Cell Carcinoma of the Bladder

Lamm et al's study was published in 1994 and involved 65 patients with biopsy confirmed transitional cell carcinoma of the bladder.[10] All patients were randomized to receive intravesical bacillus Calmette-Guerin (BCG) with or without percutaneous administration, and were additionally randomized to receive micronutrients in recommended dietary allowance (RDA) doses versus RDA doses plus therapeutic amounts of vitamins A, B_6, C, E, and zinc (**Table 4,** below). No additional supplementation with natural health products was permitted during the duration of the study. Patients were evaluated by cystoscopic examination at 3-month intervals for two years, 6-month intervals for two years, and then annually thereafter. The overall follow-up averaged 45 months (first patient enrolled in the study on August 26, 1985, and the closure of the study occurred on September 1, 1992). Thirty patients were randomized to receive RDA doses of micronutrients and 35 patients received the RDA doses plus therapeutic amounts of micronutrients. The mean patient ages were 68.1 years and 65.9 years in the RDA and RDA doses plus therapeutic amounts groups respectively.

When the data was analyzed, the results did not show that the percutaneous administration of BCG significantly reduced tumour recurrence. According to Lamm et al, 88% of patients with this type of cancer typically experience tumour recurrence when followed long-term. In their study, however, there were significant reductions in tumour recurrence rates after 10 months of treatment. After one year on treatment, the RDA doses group had 11 recurrences (37%) compared to three recurrences (9%) in the RDA doses plus therapeutic amounts group (p=0.008, Fisher's

Table 4. Daily Micronutrients (RDA Doses and RDA Doses plus Therapeutic Amounts) Administered to Patients with Transitional Cell Carcinoma of the Bladder

Micronutrients	RDA	RDA Doses plus Therapeutic Amounts of Selected Micronutrients (*)
Vitamin A acetate	5,000 IU	40,000 IU*
Vitamin B_1	1.5 mg	1.5 mg
Vitamin B_2	1.7 mg	1.7 mg
Vitamin B_3	20 mg	20 mg
Vitamin B_5	10 mg	10 mg
Vitamin B_6	2 mg	100 mg*
Vitamin B_{12}	6 mcg	6 mcg
Vitamin C	60 mg	2,000 mg*
Vitamin D_3	400 IU	400 IU
Vitamin E	30 IU	400 IU*
Folic Acid	400 mcg	400 mcg
Zinc	15 mg	90 mg*

exact test). Fifty-three percent of patients in the RDA doses had two or more episodes of tumour recurrence compared to 29% in the RDA doses plus therapeutic amounts group (p=0.0375, 1-tailed and p=0.0745, 2-tailed Fisher's exact tests). In addition, the 5-year estimates of tumour recurrences were 91% and 41% in the RDA doses and RDA doses plus therapeutic amounts groups respectively (p=0.0014, Mantel-Cox test for interval to recurrence). The overall recurrence rate for each of the micronutrient groups were 80% (24 of 30 patients) in the RDA doses and 40% (14 of 35 patients) in the RDA doses plus therapeutic amounts groups respectively. Unfortunately, the overall patient survival rates did not differ significantly between the micronutrient groups. While the mean interval to death was not statistically significant between the micronutrients groups, the RDA doses group mean interval was 18.6 months compared to 33 months among the patients in the RDA doses plus therapeutic amounts group.

With respect to side effects, no severe adverse reactions were reported in this study except stomach upset among some patients in the RDA doses plus therapeutic amounts group which generally resolved when the micronutrients were taken with food. Lamm et al concluded that the addition of high-doses of specific micronutrients to RDA doses reduced the risk of tumour recurrence in patients with transitional cell carcinoma of the bladder.

Lockwood et al's Micronutrient Treatment Approach to Breast Cancer

In this open-label trial, 32 patients (age ranges: 32 and 81 years) with high-risk breast cancer were provided with specific micronutrients (**Table 5,** p.11) and then their progress was followed for 18 months.[11]

All the patients were provided with standard oncologic care (i.e., surgery, chemotherapy, radiation, and in some circumstances Tamoxifen) and were evaluated every three months in order to detect any recurrence of cancer. In all cases, the breast cancers had spread to the lymph nodes, but some patients had metastases at different locations, such as the skin, the pleura or in the thoracic vertebrae. Whole blood coenzyme Q_{10} levels were taken at 0, 3, and 12 months (27 patients), and a random subgroup (10 patients) had more extensive haematological, immunological, and micronutrient testing.

The mean coenzyme Q_{10} levels were significantly higher at 3-12 months compared to baseline ($p<0.01$). The mean baseline coenzyme Q_{10} level was 0.82 ug/ml compared to mean levels of 1.45 ug/mL and 1.60 ug/ml at three and 12 months respectively. Lockwood et al noted that the reference range of coenzyme Q_{10} among people without overt disease is typically between 0.5-1.5 ug/mL, which led them to conclude that the coenzyme Q_{10} supplementation provided to their patients was too low. They noted that in only 6 of 27 patients did the blood levels of coenzyme Q_{10} exceed 1.5 ug/mL (maximum level achieved was 2.81 ug/mL). Other statistically significant mean increases at 12 months compared to mean baseline levels were seen with beta-carotene, vitamin E, vitamin B_6, and selenium. In addition, there were statistically significant increases in mean natural killer cell counts and lymphocyte cell counts when the 12 month mean values were compared to the three month mean values of these immunological parameters ($p<0.05$ for both).

In six patients partial tumour regression resulted. Not one of the 32 patients died during the 18 months of follow-up. From a statistical point of view Lockwood et al noted that at least four patients should have died during the 18 months of follow-up. In all patients, there was no weight loss, the need for painkillers was reduced, quality of life improved, and there were no signs of progression of eventual metastases. The only side effect noted was increased yellowing on the palms, and the odd fishy taste experienced by some patients.

In a follow-up report[12] some 24 months from the beginning of the open-label trial, all 32 patients remained physically well and none had died. The dose of coenzyme Q_{10} was increased to 390 mg/day in one of the six patients who experienced partial tumour regression. In this particular patient, her tumour became non-palpable one month following the

Table 5. Daily Micronutrients Administered to Patients with High-Risk Breast Cancer

Vitamins and Fatty Acids	Daily Doses
Vitamin A	2,500 IU
Beta Carotene	32,500 IU
Vitamin E (D-alpha tocopherol)	2,500 IU
Vitamin B_1	15 mg
Vitamin B_2	15 mg
Vitamin B_3 (niacin)	45 mg
Vitamin B_5	22 mg
Vitamin B_6	75 mg
Vitamin B_{12}	13 mcg
Vitamin C	2,850 mg
Vitamin D	300 IU*
Folic Acid	300 mcg
Biotin	300 mcg
Coenzyme Q_{10}	90 mg
Gamma-linolenic acid	1,200 mg
Omega-3 Essential Fatty Acids	3,500 mg**
Trace Elements	
Magnesium	150 mg
Copper	3 mg
Manganese	6 mg
Zinc	22 mg

*The type of vitamin D was not provided.
**The composition of omega-3 essential fatty acids was not provided.

increase, and at the 2-month mark mammography confirmed the absence of tumour (i.e., complete regression). Another patient with breast cancer had a residual tumour following non-radical breast cancer surgery. In this case, three months of 300 mg/day of coenzyme Q_{10} resulted in the patient being in excellent clinical condition and having complete regression of the residual tumour.

In another report,[13] an additional three patients with breast cancer were provided with standard oncologic care and 390 mg/day of coenzyme Q_{10} for 3-5 years. In a 44-year-old patient, her numerous liver metastases disappeared and there was no evidence of metastases elsewhere. In a 49-year-old patient, there were no signs of tumour in her pleural cavity following 6 months of treatment. In a 75-year-old patient, there was no evidence of cancer in the tumour bed or metastases following lumpectomy and coenzyme Q_{10} treatment. In 2 of the patients, measurements of coenzyme Q_{10} showed significant increases from baseline with levels at or above 3.34 ug/mL, with the highest level attained from treatment being 3.77 ug/mL.

Hertz's and Lister's Micronutrient Treatment Approach to Patients with End-Stage Cancer

This pilot study assessed patients with end-stage cancer taking micronutrients (i.e.,

coenzyme Q_{10}, vitamins, selenium, and essential fatty acids) during 9 years (**Table 6**, below).[14]

Forty-one patients with end-stage cancer were included, and 40 of them were followed until they died. One patient was lost to follow-up, but was presumed to have died. The primary cancers involved the breast, brain, lungs, kidneys, pancreas, esophagus, stomach, colon, prostate, ovaries and skin. The median survival times of the patients on micronutrients were compared to median predicted survival times calculated from Kaplan-Meier curves of patients not on micronutrients. The median predicted survival was 12 months (range: 3-29 months), whereas the actual median survival was 17 months (range: 1-120 months); a greater than 40% median predicted survival. The actual mean survival was 28.8 months compared to 11.9 months for the mean predicted survival of patients not on these micronutrients. In total, 10 patients (24%) survived for less time than predicted, whereas 31 of them (76%) survived for a longer duration than predicted. Hertz and Lister did not provide a robust explanation for why 10 patients survived for less time than predicted. They did note, however, that starting micronutrients within 1.5 months of being diagnosed with metastases or being declared incurable conferred much longer survival times (i.e., a median predicted survival of seven months in excess of predicted survival times) compared to patients that started the micronutrients after 1.5 months (i.e., a median survival time of 1.5 months in excess of predicted survival times). It is possible that some of the patients that lived less than the predicted survival times might have initiated micronutrient treatment later than those patients that lived longer than predicted. Overall, the micronutrient treatment was well tolerated and the investigators noticed that a large majority of the patients had an impressive improvement in their sense of wellbeing commencing with the micronutrient treatment.

Table 6. Daily Micronutrients Administered to Patients with End Stage Cancer

Vitamins and Fatty Acids	Daily Doses
Vitamin C	5,700 mg
Vitamin E (D-alpha tocopherol)	1,625 mg
Coenzyme Q_{10}	300 mg
Selenium (as selenomethionine)	487 mcg
Folic acid	5 mg
Vitamin A	25,000 IU
Beta-carotene (lung cancer patients excluded)	76 mg
Gamma-linoleic acid	375 mg
Fish oil	1,500 mg*
Vitamin B_1	5.4 mg
Vitamin B_2	8.4 mg
Vitamin B_3 (niacin)	45 mg
Vitamin B_5	22.5 mg
Vitamin B_6	12.6 mg
Vitamin B_{12}	13.5 mcg

*The composition of omega-3 essential fatty acids was not provided.

Discussion

In five of the six studies that combined standard oncologic care with broad-spectrum micronutrients, high-risk, terminally ill, or end-stage cancer patients lived better and/or longer (**Table 7**, p.14).

Given the fact that micronutrients appear to work better when taken soon after diagnosis and among patients with better prognoses, it seems wise to recommend some combination of micronutrients to cancer patients following diagnosis. Based on all the data reviewed in this paper, I have created a table with suggested daily dose ranges of the various micronutrients used in the cited studies so that clinicians can feel comfortable when individualizing them to their patients with cancer (**Table 8**, p15).

There were no significant or worrisome adverse reactions to the micronutrients, except for the rare occurrence of gastrointestinal upset. Many of the studies showed that patients experienced better physical wellbeing, improved quality of life, and fewer side effects or complications from standard oncologic care when taking the micronutrients.

It is nearly impossible to isolate which micronutrient factor(s) were involved in the positive results. There are, however, several biochemical findings that are worthy of more discussion. In one of the studies the baseline (i.e., pre-treatment) whole blood zinc levels were higher among patients with SCLC that remained alive compared to patients with SCLC that succumbed during the evaluation period.[9] These results seem to be unaffected by supplemental zinc since all patients in the SCLC study were given approximately 27-45 mg of elemental zinc daily. Zinc levels (in whole blood and/or plasma), and copper-to-zinc ratios have been investigated for having some predictive value in prognosis and/or treatment response. In a study involving patients (n=13) with squamous cell carcinoma of the head and neck, measurements of zinc in the plasma and whole blood were decreased and the copper-to-zinc ratio was significantly higher compared to controls.[16] This same study also found that plasma zinc was significantly lower among patients who were unresponsive to therapy and who died within 12 months compared to patients who responded to therapy and experienced remission within 12-15 months. This is consistent with the results of the SCLC study.

In another study involving 44 patients with recently diagnosed and untreated haematological malignancies, the mean serum zinc level was significantly higher in healthy controls compared to the patients with cancer and the mean copper-to-zinc ratios were significantly lower among the healthy controls compared to the patients with cancer.[17] Just like in the SCLC study, the patients who survived during a mean follow-up period of 13 months had mean serum zinc levels that were higher than those patients who died during the same follow-up period. It is conceivable that some of the benefits observed among some of the patients taking micronutrients might be associated with higher pre-treatment (i.e., baseline) plasma and/or whole blood zinc levels even though it was only assessed in one of the six reviewed studies.

Another biochemical finding worth discussing involves blood levels of coenzyme Q_{10}. In the Lockwood et al study patients with high-risk breast cancer were prescribed 90 mg of coenzyme Q_{10}, and the blood levels of coenzyme Q_{10} in only six out of 27 patients exceeded 1.5 ug/mL (maximum level reached was 2.81 ug/mL).[11] In a follow-up to that original study, when three more patients were given increased amounts of daily coenzyme Q_{10} (i.e., 390 mg/day), complete remissions resulted over a treatment period of 3-5 years.[13] Blood levels of coenzyme Q_{10} among two of these patients showed marked elevations from baseline (0.83-0.97 ug/mL and 0.62 ug/mL) resulting from treatment (3.34-3.64 ug/mL and 3.77 ug/mL). Hoffer also advised many of his patients from the original study[8] to take 300 mg/day of coenzyme Q_{10} until they went into remission, with instructions to decrease the dose to 100-150 mg/day thereafter. Unfortunately, Hoffer did not specifically identify the exact number of patients taking this micronutrient nor did he publish any blood levels on such

Table 7. Summary of Studies Combining Broad-Spectrum Micronutrients and Standard Oncologic Care

Study	Cancer Populations Studied	Main Outcomes
Hoffer & Pauling[6]	Terminally ill cancer patients	Improved mean survival times - mean survival time of non-random controls was 5.7 months (n=31) compared to a mean survival time of 92 months (n=81) among patients who followed the combined treatment. Sixteen years after the study began, 34 (about 34%) of those patients from the combined treatment group were still alive, while all of the patients (0%) who had received standard oncologic care had died.[8]
Hoffer & Pauling[7]	Terminally ill cancer patients	No differences in mean survival times between non-random controls and cancer patients.
Jaakkola et al[9]	Small-cell lung cancer patients	Improved 2-year survival - patients given combination treatment had a 2-year survival rate of 33% (n=6) compared to 2-year survival rare that is usually less 15%.
Lamm et al[10]	Patients with transitional cell carcinoma of the bladder	Reduction in tumour recurrence –the 5-year estimate of tumour recurrence in this study was 41% (in the RDA doses plus therapeutic amounts group) compared to an expected 88% of tumour recurrence during long-term follow-up.
Lockwood et al[11]	High-risk breast cancer patients	Improved survival – none of the 32 patients on combined treatment died during 18 months of follow-up compared to estimates showing that at least 4 patients should have died during the follow-up period. Twenty-four months from the beginning of the open-label trial, all 32 patients remained physically well and none had died.[12]
Hertz and Lister[14]	Patients with end-stage cancer	Improved survival - The mean survival was 28.8 months for patients on micronutrients compared to a mean predicted survival of 11.9 months for patients not on micronutrients. Ten patients (24%) survived for less time than predicted, whereas 31 of them (76%) survived for a longer duration than predicted.

Table 8. Suggested Daily Dose Ranges of Micronutrients Administered to Patients with Cancer

Vitamins and Essential Fatty Acids	Daily Doses
Vitamin A:	2,500-50,000 IU
Beta Carotene: (lung cancer patients excluded)	10,000-130,000 IU
Vitamin E (D-alpha tocopherol)	30-2,500 IU
Vitamin B_1	15-750 mg
Vitamin B_2	15-50 mg
Vitamin B_3 (niacin or niacinamide)	20-3,000 mg
Vitamin B_5 (calcium pantothenate)	10-300 mg
Vitamin B_6	75-1,140 mg
Vitamin B_{12} (cyanocobalamin or other forms of the vitamin if preferred)	13-1,600 mcg
Vitamin D_3 (cholecalciferol):	400-1,000 IU
Vitamin C	60-12,000 mg
Biotin	300-10,000 mcg
Coenzyme Q_{10}	300-400 mg*
Gamma-linolenic acid	375-1,200 mg
Omega-3 essential fatty Acids (contains eicosapentaenoic and docosahexaenoic acids)	5,000 mg or more
Trace Elements (all doses in elemental quantities)	
Calcium	500-1,000 mg
Chromium	800-3,200 mcg
Copper	0-3mg
Magnesium	150-500 mg
Manganese	0-200 mg
Potassium	0-120 mg
Selenium	200-3,400 mcg
Vanadium	0-800 mcg
Zinc	15-220 mg

*The ubiquinol form of coenzyme Q10 is preferred based on better absorption and perhaps better therapeutic results as per data obtained from patients with congestive heart failure.[15]

patients. Likewise, in the Hertz and Lister study,[14] all the end-stage cancer patients were prescribed 300 mg/day of coenzyme Q_{10} and the overall results were very favourable. It is unfortunate that the blood levels of coenzyme Q_{10} were also not provided in the Hertz and Lister study.

It appears important for clinicians to consider obtaining baseline coenzyme Q_{10} levels on their patients prior to prescribing various combinations of micronutrients. As was apparent in the Lockwood et al study,[11] a 90 mg/day dose of coenzyme Q_{10} was insufficient in producing blood levels likely to

confer significant anti-cancer effects. Daily doses in the range of 300-400 mg seem more capable of conferring anti-cancer effects since such doses produce blood levels of coenzyme Q_{10} that are greater than the usual reference ranges for this micronutrient. (In Ontario, Canada, the reference range used by Gamma-Dynacare Medical Laboratories for coenzyme Q_{10} levels for adults from a normal population is 0.37-2.20 ug/mL). Blood levels of coenzyme Q_{10} that were associated with remissions among three patients with high-risk breast cancer were at or above 3.34 ug/mL.[13] Thus it makes sense for any micronutrient program to include daily amounts of coenzyme Q_{10} at or above 300 mg.

The type of coenzyme Q_{10} is likely clinically important as well. In the cited studies the ubiquinone form of coenzyme Q_{10} was used. This form is inferior to the ubiquinol form, which should be the preferred type prescribed to cancer patients. Based on data obtained from a study involving patients with congestive heart failure, the clinical and plasma (i.e., absorption) differences between both forms of coenzyme Q_{10} were evaluated.[15] When patients with congestive heart failure took 900 mg/day of ubiquinone they showed limited clinical improvement and their plasma coenzyme Q_{10} levels were less than 2.5 ug/mL. When 7 patients with advanced congestive heart failure were given an average dose of 580 mg/day of ubiquinol, their mean plasma levels of coenzyme Q_{10} jumped from a baselines level of 1.6 ug/mL (SD: 0.9-2.0 ug/mL) to 6.5 ug/mL (SD: 2.6-9.3 ug/mL). With the increased absorption of coenzyme Q_{10} (i.e., increased plasma level), these patients showed both clinical improvement and enhancement of left ventricular function. It seems prudent, therefore, to prescribe daily doses of ubiquinol to patients having cancer that are equal to or greater than 300 mg.

It is most likely that the benefits seen in five of the six studies were the result of the synergistic effects of the multiple micronutrients prescribed. There are many possible ways in which combinations of micronutrients improve health and/or increase lifespan among patients with cancer. Some of them might involve the inducement of differentiation, proliferation inhibition, and apoptosis.[18] These growth-inhibiting effects might have less to do with their antioxidant action, and more to do with changes in gene expression as well as the levels of proteins and translocation of specific proteins from one cellular compartment to another.[18] Combinations of micronutrients might benefit cancer patients by quenching free radicals generated by cancer cells, thereby reducing the creation of new cancerous mutations, which would possibly increase the therapeutic efficacy (i.e., by reducing treatment resistance) of cancer treatment through standard oncologic care.[19]

A number of extensive review articles have also shown that the combined use of antioxidants and other micronutrients consistently result in less chemotherapy-related toxicity[20] and no interference with standard oncologic care, while also enhancing the killing capacities of oncologic modalities, decreasing their side-effects, and protecting normal tissue from damage.[21,22] These findings are in stark contrast to some of the more conservative views expressed, such as the one by Sagar,[23] in which the interactions are viewed as complex, unpredictable, potentially harmful as a result of reducing the cytotoxicity of chemotherapeutic agents, and impacting negatively upon the sensitive pharmacokinetics of chemotherapeutic drugs. Sagar is also concerned about the impact that micronutrients might have upon radiotherapy by their capacity to replenish total antioxidant status and reduce the expected normal-tissue toxicity from this mode of cancer therapy. Even though there appears to be robust evidence showing that the combined use of micronutrients with standard oncologic care is safe and often effective, at the present time there continues to be much resistance to this approach and more often than not patients are dissuaded from combining micronutrients with standard oncologic care by their oncologists.

Conclusion

There are more questions than answers about the combined use of micronutrients and standard oncologic care. For example,

could a combination of the micronutrients mentioned in this paper be used to prevent cancer, or prevent secondary cancers (or recurrences) once primary cancers are in complete clinical remission? Not having such answers gives credence to many papers (see Sagar,[23] for example) that typically state in some manner or another that only phase III trials can determine the relative advantages of a combined approach. Such papers also highlight the potential negative impacts between micronutrients and standard oncologic care, and remark that until these high-quality studies are done, we will not be able to make appropriate clinical decisions since current clinical facts are based too much upon theory and even ignorance.

It is true that all of the studies cited in this review, except for one double-blind clinical trial,[10] were not of the highest quality and relied on some combination of non-random or historical (i.e., statistically calculated) controls. Even though all of these factors do introduce potential bias, it cannot be disputed that most of the patients taking combinations of micronutrients with standard oncologic care did in fact live better and/or longer. These findings merit attention since patients taking the combination of micronutrients and standard oncologic care had very poor prognoses. It is ignorant and potentially harmful for clinicians simply to wait until high-level evidence exists before providing such patients with the available information and letting them decide how they wish to proceed.

Competing Interests

The author declares that he has no competing interests.

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