VOLUME 22 · NUMBER 21 · NOVEMBER 1 2004

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Efficacy of Coenzyme Q10 for Improved Tolerability of Cancer Treatments: A Systematic Review

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Submitted February 4, 2004; accepted August 23, 2004.

Supported by a grant from the British Medical Association (L.R.) and the Pilkington Family Trusts (K.S.).

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/04/2221-4418/$20.00

DOI: 10.1200/JCO.2004.02.034

ABSTRACT

Purpose
The aim of this systematic review was to summarize and evaluate the evidence available for oral supplementation with coenzyme Q10 (CoQ10) to improve the tolerability of cancer treatments.

Materials and Methods
Searches for all published and unpublished controlled trials were carried out on seven databases. Manufacturers of CoQ10 were identified and contacted. Controlled clinical trials of monopreparations of CoQ10 administered orally to cancer patients were included. No language restrictions were imposed. Data were extracted independently by two authors according to predefined criteria.

Results
Six studies were included in the review, including three randomized clinical trials and three nonrandomized clinical trials. Patients in five of six studies received anthracyclines. The results suggested that CoQ10 provides some protection against cardiotoxicity or liver toxicity during cancer treatment. However, because of inadequate reporting and analysis, as well as questionable validity of outcome measures, the results are not conclusive.

Conclusion
Suggestions that CoQ10 might reduce the toxicity of cancer treatments have not been tested by rigorous trials. Further investigations are necessary to determine whether CoQ10 can improve the tolerability of cancer treatments.

J Clin Oncol 22:4418-4424. © 2004 by American Society of Clinical Oncology

INTRODUCTION

Complementary and alternative medicine (CAM) has become an important issue among cancer patients. The inability of conventional medicine to treat all aspects of cancer and the patients' desire for an active role in the decision-making process regarding their treatments have been regarded as some of the contributing factors as to why CAM has become more popular over the last decades.[1-3]

A systematic review of surveys on the topic included 26 investigations, from 13 countries, published between 1977 and 1998. The average prevalence of CAM usage in cancer patients was reported to be 31%.[4] A more recent survey of 148 breast cancer patients in the state of Vermont reported considerably higher prevalence figures; 62.8% reported using at least one CAM treatment after surgery, with vitamins and nonfood supplements being the most frequently used.[5]

The widespread and well-documented use of CAM by cancer patients has led to a need for intensive research focused on the efficacy and safety of some of the CAM modalities. Coenzyme Q10 (CoQ10), also known as vitamin Q10, ubiquinone, or ubidecarenone, is one of the top 10 complementary therapies being promoted on the

Internet for cancer care.[6] A Danish survey of 769 cancer patients found that 18% used CoQ10.[7]

A coenzyme is an organic, nonprotein molecule that binds with a protein molecule to form an active enzyme. The formula of CoQ10 ($C_{59}H_{90}O_4$) is synthesized endogenously in humans and is also found in virtually all aerobic organisms.[8] The primary action of CoQ10 occurs in the electron transport chain for cellular respiration. It is a lipid-soluble quinone and is essential for the synthesis of adenosine 5′-triphosphate (ATP). It affects the function of all cells in the body in its role as a mobile electron transporter, assisting enzymes in the oxidation of nutrients in the mitochondria of cells to produce energy for growth and preservation.[9] CoQ10 is also metabolized to ubiquinol, which prolongs the antioxidant effect of vitamin E.[10]

CoQ10 is widely promoted for enhancing or modulating the immune system. Levels of immunoglobulin G in serum of patients treated with CoQ10 have been found to increase,[11] and in 1993, a small uncontrolled trial on healthy participants suggested that CoQ10 supplementation may help support immune responses by increasing immunoglobulin G and T4/T8 lymphocytes.[12] Other uncontrolled studies have suggested that CoQ10 may suppress tumor growth.[13-15] However, no controlled trials have been published assessing the use of CoQ10 alone as a prevention or treatment for cancer in humans.

CoQ10 is manufactured as a dietary supplement by the fermentation of beets and sugarcane with yeast and is taken widely in Japan. In the diet, it is primarily derived from meat and poultry.[16] After absorption in the gastrointestinal tract, CoQ10 is distributed to the liver and incorporated into very low–density lipoproteins.[9] Serum concentrations of CoQ10 have been found to increase after ingestion of CoQ10 both as a supplement and postprandially.[16] It is absorbed well but slowly from dietary and supplementary sources, with peak plasma levels occurring 5 to 10 hours after ingestion.[9]

Deficiencies of CoQ10 in humans occur with age, the use of certain medications, and with diseases including cancer.[17] The incidence of CoQ10 deficiency has been found to be significantly higher in cancer patients than in healthy controls.[18] In a study of 200 women hospitalized for breast cancer surgery, a CoQ10 deficiency was noted both in patients with malignant (80 patients) and nonmalignant lesions (120 patients).[19] Serum levels of CoQ10 may be depleted by 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors (including lovastatin), which are usually used for lowering cholesterol.[17]

Anthracyclines, commonly used in chemotherapeutic regimens, have been shown to interfere with the energy-generating biochemical actions of CoQ10[20,21] and to generate free radicals, which affect cell growth and tumor production. CoQ10 is a free-radical scavenger, and its antioxidant activity and membrane-stabilizing properties help to protect against and repair damage to DNA caused by free radicals. The impact of free radicals on DNA is thought to be the link between free radicals and cancer formation.[22]

Anthracyclines are also known to cause cardiotoxicity.[23,24] Acute toxicity is usually manifested by changes in ECG, including arrhythmias, but delayed dose-related cardiomyopathy can also occur, resulting in congestive heart failure.[24] CoQ10 supplementation can have favorable actions in various cardiovascular conditions[8]; thus, studies have investigated the use of CoQ10 for reducing the adverse effects of cancer treatments and have particularly focused on the cardioprotective effect of CoQ10 in cancer patients treated with anthracycline antibiotics.

The aim of this systematic review is to summarize and critically evaluate the available evidence for or against the efficacy of supplementation with CoQ10 for improved drug tolerability in cancer patients.

MATERIALS AND METHODS

Electronic literature searches were performed to identify all controlled clinical trials in which CoQ10 was administered to cancer patients. The following electronic databases were searched from their inception until July 2003: the Allied and Complementary Medicine Database (inception 1985), the British Nursing Index (1994), CINAHL (1983), DH-DATA (1983), EMBASE (1966), MEDLINE (1966), and the Cochrane Central Register of Controlled Trials. The search terms used were cancer or oncolog$ or carcinogen$ or tumo$r and ubiquinone or ubidecarenone or coenzyme Q10 or CoQ10 or CoQ 10 or CoQ-10 or Co-Q10. Additional hand searches were carried out on the bibliographies of the obtained articles and on our departmental files.

Twenty-eight manufacturers from five countries were sent letters requesting details of any clinical trials they may have conducted with CoQ10 on cancer patients. Three manufacturers replied, all stating that they had not conducted trials of this nature.

No restrictions were placed on the language of publication. Studies were included only if they were controlled trials in which monopreparations of CoQ10 were administered orally to cancer patients in addition to standard cancer care. Studies were excluded if they measured CoQ10 levels rather than clinical effects of CoQ10 supplementation. Reviews were also excluded after the bibliographies were searched for more trials. Figure 1 shows the inclusion and exclusion process.

Papers were translated in house by other researchers where necessary, and data was extracted independently from each study by two reviewers (L.R., K.S.) according to predefined criteria. The methodologic quality of studies was assessed using the Jadad score.[25] The Jadad score is calculated by assessing the following three criteria: methods of blinding, randomization, and reporting of dropouts and withdrawals. The maximum number of points that can be achieved on the Jadad score is 5. The heterogeneity of the studies precluded statistical pooling of the results. Therefore, they were tabulated and described narratively.

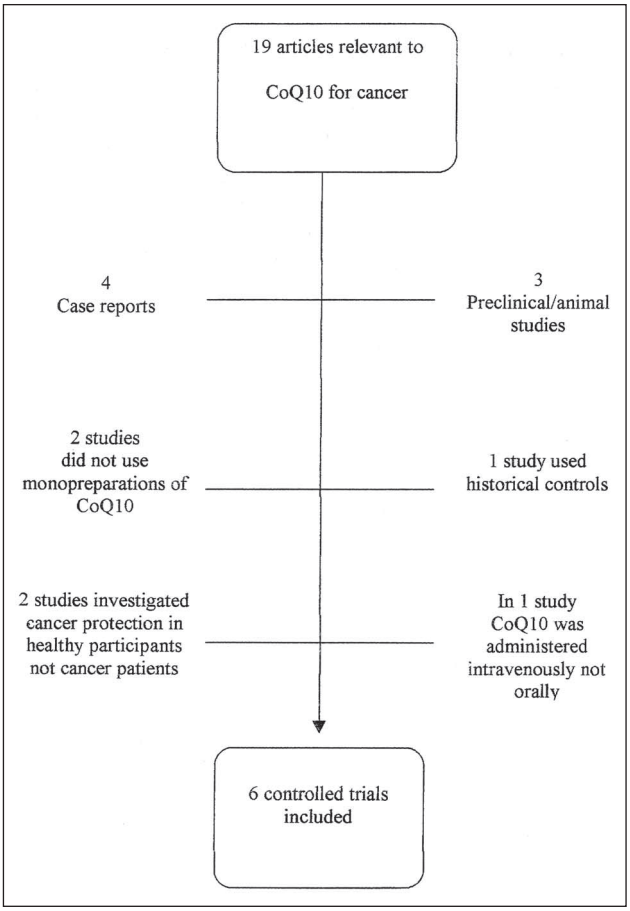

Fig 1. Flowchart of excluded studies. CoQ10, coenzyme Q10.

RESULTS

Nineteen studies were retrieved in the literature searches. Six trials met our inclusion criteria. Two studies were excluded because of the administration of combined treatments consisting mainly of CoQ10, vitamin C, vitamin E, beta-carotene, selenium, and zinc.[26,27] The extracted data of the six studies that met our criteria[28-33] are listed in Table 1.

The included studies were carried out in Japan,[28-30] Italy,[31,32] and the United States[33] between 1982 and 1996. Three of the studies were randomized controlled trials.[29-31] There was one placebo-controlled double-blind study.[28] All other studies were open trials in which the experimental group received CoQ10 plus standard care and controls received standard care only. Sample sizes ranged from 19 to 88 patients, and dropouts and withdrawals were mentioned in two studies.[32,33] All participants included in the studies had previously been diagnosed with various types of cancer. The ages of participants were reported in all but one study and varied widely across the studies (range, 1 to 71 years). One study included children.[31] Sex was not specified in two studies,[28,30] but all other studies included both male and female patients.

Studies examined the protective effect of CoQ10 against toxic adverse effects of cancer drug treatment and whether CoQ10 improved the tolerance of anthracyclines or other cancer treatments. This was assessed using various measures of heart function and toxicity in five studies[29-33] and using hair loss and liver enzyme levels in one study.[28] Cancer treatment included anthracyclines in all the studies except one, in which patients were treated with lovastatin.[33] The CoQ10 dosage ranged from 90 mg/d to 240 mg/d. Although daily recommended allowance has not yet been established for CoQ10, manufacturers advise a daily intake between 10 and 100 mg. No toxicity has been reported for daily intakes as high as 300 mg. However, safety has not been established in pregnant or lactating women.

The duration of treatment with CoQ10 varied according to an individual's cancer treatment. No adverse effects of CoQ10 were reported in any of the studies. None of the included studies recorded survival outcomes or measured changes in tumor responses. The individual studies are narratively described in the following paragraphs.

Akihama et al[28] investigated the protective effect of CoQ10 against hair loss and abnormalities of liver enzymes during treatment with anthracycline antibiotics in a double-blind, placebo-controlled trial. Nineteen participants diagnosed with acute leukemia, blastic crisis of chronic myeloid leukemia, or malignant lymphoma were included. Eight participants received 120 mg/d CoQ10. No significant differences were found in hair loss between the experimental group and the placebo group. It was suggested that this might be a result of low absorption of CoQ10 when administered orally. Serum levels of AST increased significantly in the placebo group ($P < .01$) but not in the treatment group.

Iarussi et al[31] conducted a randomized controlled trial of the protective effect of CoQ10 on anthracycline cardiotoxicity. Ten of 20 children with acute lymphoblastic leukemia or non-Hodgkin's lymphoma were given 100 mg of CoQ10 twice daily. Myocardial function was measured using echocardiography. Measurements were taken at baseline, at a cumulative dose of 180 mg/m^2, and at the end of treatment. A significant reduction in percentage of left ventricular fractional shortening was noted in both the CoQ10 and the control groups between baseline measurements and the end of treatment with anthracyclines. In the control group, a reduction in percentage of left ventricular fractional shortening appeared earlier than in the experimental group. However, in the experimental group, no significant changes in left ventricular fractional shortening were found. A significant reduction in interventricular septal wall thickening was noted in the control group only. No significant changes were found in left ventricular posterior wall thickening in either group. The authors suggest that CoQ10 had a protective effect on left ventricular global function and

Table 1. Controlled Clinical Trials of Orally Administered Coenzyme Q10 for Improved Tolerance of Cancer Treatments

Reference	Design	Jadad Score	No. of Patients	Participants: Type of Cancer	Participants: No.	Cancer Treatment and Dosage	CoQ10 Dosage	Primary Outcome Measures	Within-Group Results	Between-Group Results
Akihama et al[28]	CCT	2	19	Acute leukemia Blastic crisis of chronic myeloid leukemia Malignant lymphoma	6 2 11	Anthracycline antibiotics: doxorubicin (n = 11) or daunomycin (n = 8); cumulative dose: 50-100 mg	120 mg/d for 2-6 months	Hair loss; serum level of AST and ALT liver enzymes	Both enzymes levels raised in the placebo group ($P < .01$); no significant differences in CoQ10 group	No significant differences in hair loss or enzyme levels between groups; no protection against hair loss
Iarussi et al[31]	RCT	2	20	Acute lymphoblastic leukemia Non-Hodgkin's lymphoma	17 3	Anthracylines; cumulative dose: CoQ10 group, 240 ± 20 mg/mg^2; control group: 252.0 ± 20.1 mg/mg^2	100 mg bid, duration not stated	Cardiotoxicity/myocardial function (echocardiography): % LVFS; SWT; LVPWT	Significant reduction in % LVFS in both groups: CoQ10 group: $P < .05$; control: $P < .002$ (change earlier in control group); significant reduction in SWT in control group ($P < .01$); NS changes in LVPWT	LVFS reported to be significantly lower in CoQ10 group, but no statistics reported
Lucarelli et al[32]	CCT	1	30	Hematologic neoplasm	30	Complex cytostatic therapy: anthracyclines: daunoblastin, doxorubicin, 50-80 mg for 3-5 days	30 mg Ubiten tid for 30 days	SBP; DBP; ECG: QRS voltage; frequency of repolarization alterations; heart rate	Increase in SBP in CoQ10 group significant at $P < .05$; increase in DBP in CoQ10 group only; ECG remained normal in CoQ10 group; QRS lowered in two patients in control group	No between-group results reported
Okuma et al[29]	RCT	1	80	Lung cancer Malignant lymphoma Patients with nine other types of solid tumour cancers	30 30 20	Chemotherapy including doxorubicin	90 mg/d, 1 week before chemotherapy until chemotherapy completed	Cardiotoxicity (ECG); QRS voltage; QTc duration	CoQ10 group remained stable	QRS voltage lower in control group at measurements 1, 2, and 3 ($P < .01$); QRS duration longer in control group at last treatment ($P < .05$); QTc duration was significantly longer in control group at measurements 5, 6, and 7 ($P < .05$) and at measurement 8 ($P < .01$)
Takimoto et al[30]	RCT	1	40	Lung Breast Thyroid All treated with doxorubicin	33 6 1	FAC therapy every 3 weeks: day 1, 500 rad irradiation of cobalt 60; day 2, 500 mg flurouracil + 50 mg doxorubicin + 500 mg cylcophosphamide	90 mg/d; duration not stated	Myocardial intoxication; CTR Pulse rate; ECG: QRS voltage	CTR and pulse rate increased in control group (no statistics reported)	Significant difference in CTR increase between control and CoQ10 group ($P < .01$); CTR increased significantly more in control group; NSD in pulse rates; NSD in QRS voltage
Thibault et al[33]	CCT	1	88	Hormone-independent prostate Primary CNS Breast Colorectal Ovary Sarcoma Lung Others	38 24 7 4 4 3 2 6	Lovastatin administered at four different dose levels: (30, 35, 40, or 45 mg/kg/d)	240 mg/d ubiquinone in four doses administered with lovastatin; duration not stated	Toxicity: National Cancer Institute Common Toxicity Criteria + musculoskeletal toxicity (myalgias); drug activity: cholesterol concentrations; Serum HMG-CoA reductase inhibitory activity	Declined rapidly in both groups (CoQ10 did not affect drug activity)	CoQ10 did not decrease the incidence of musculoskeletal toxicity but significantly reduced its severity ($P < .01$); NSD between groups; NSD between groups

Abbreviations: CoQ10, coenzyme Q10; CCT, controlled clinical trial; CTR, cardiothoracic ratio; NSD, no significant difference; QRS, deflections in an ECG that represent ventricular activity of the heart; QTc, correction of time from ECG Q wave to the end of the T wave corresponding to electrical systole; RCT, randomized controlled trial; % LVFS, percentage of left ventricular fractional shortening; SWT, septum wall thickening; LVPWT, left ventricular posterior wall thickening; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant; FAC, fluorouracil, doxorubicin, cyclophosphamide; HMG-CoA, 3-hydroxy-3-methylglutaryl–coenzyme A.

was effective in protecting myocardial function during therapy with anthracyclines.

In an open, controlled, clinical trial, Lucarelli et al[32] investigated the effect of CoQ10 on toxic cardiopathy from antiblastic therapy with the anthracycline duanoblastine. Fifteen of 30 patients diagnosed with hematologic cancers took 30 mg CoQ10 tid (Ubiten; Italfarmaco, Milan, Italy) for 30 days. Blood pressure, ECG readings, and heart rate were obtained at the beginning and the end of treatment. Systolic blood pressure measurements were taken at rest and after gentle exercise; after gentle exercise, the measurements were not significantly different in the treatment group compared with the control group, but when they were measured at rest, they increased significantly in the treatment group at the end of treatment ($P < .05$). This was attributed to an improvement in general health. The diastolic pressure increased slightly in both groups and was reported to be significant in the experimental group. The authors suggest that a positive effect of CoQ10 was demonstrated by improvements in general health and less cardiotoxicity. The ECG remained stable in more patients in the treatment group than in the control group. Nine patients in the CoQ10 group had a normal ECG reading at the beginning of treatment, and six had a normal reading at the end of treatment; whereas in the control group, seven patients had a normal reading at the beginning of treatment, and four had a normal reading at the end of treatment. No statistical analysis of this difference was reported. No significant alterations in heart rate or blood sugar were found in either group. Repolarization alterations were more frequent in the control group. No adverse effects attributable to CoQ10 were reported.

In a 13-center, randomized, clinical trial, Okuma et al[29] examined the protective effect of CoQ10 in 80 patients treated with chemotherapy including doxorubicin. Patients suffered from 10 different types of cancer, including 30 patients with lung cancer and 30 patients with malignant lymphoma. CoQ10 was administered to 39 patients at a dose of 90 mg/d beginning 1 week before chemotherapy and continuing until the treatment with doxorubicin was completed. Serial ECGs were recorded immediately before and after each administration of doxorubicin. QRS voltage decreased in the control group but increased in the CoQ10 group at treatments 1, 2, and 3. QRS duration became significantly lower in the control group than the CoQ10 group ($P < .05$). QTc duration was significantly longer and QRS voltage decreased in the control group. In patients taking CoQ10, both variables remained stable.

In 1982, Takimoto et al[30] carried out a randomized, open study investigating the effects of 90 mg/d CoQ10 on myocardial toxicity during therapy consisting of an irradiation of cobalt and an infusion of doxorubicin, cyclophosphamide, and fluorouracil. Forty patients suffering from lung, breast, and thyroid cancer received doxorubicin, cyclophosphamide, and fluorouracil every 3 weeks for 4.4 ± 3 months (experimental group) or 5.8 ± 3 months (control group). Twenty patients in the experimental group received CoQ10. Patients in the CoQ10 group showed a significant increase in their cardiothoracic ratio when compared with the control group. There were no differences between the two groups in heart rate and ECG measures, such as QRS, ST segment, T-wave, and arrhythmia frequency.

In 1996, Thibault et al[33] investigated the effect of 240 mg/d CoQ10 on 88 cancer patients enrolled onto an open, controlled, clinical trial primarily designed to measure the tolerability of lovastatin when administered at progressively higher doses to achieve antiproliferative activity. Patients suffered from various forms of cancer. Patients were treated with four different doses of lovastatin, which was administered qid for 7 days in monthly cycles. CoQ10 was administered to 56 of 88 patients to prevent lovastatin-induced myotoxicity in stage 2 of the study. Of the 56 patients, only 27 had previously been treated with lovastatin during stage 1 of the study. The remaining 32 patients were treated with lovastatin only during stages 1 and 2. The activity of lovastatin was determined using biochemical measurements of pharmacologic parameters. Musculoskeletal toxicity was assessed, and toxicity was graded according to the National Cancer Institute Common Toxicity Criteria. Tumor responses were also monitored. CoQ10 had no effect on the activity of lovastatin; cholesterol concentrations declined significantly in both groups, with no significant intergroup differences. The administration of CoQ10 did not decrease the incidence of musculoskeletal toxicity, but its severity was significantly reduced. It is unclear whether the analysis was carried out with just the 27 patients in the CoQ10 group who had previously received lovastatin or whether all 56 patients who received CoQ10 were included.

DISCUSSION

These results indicate that CoQ10 may provide some protection against toxicity associated with cancer treatments. However, weaknesses in the design and reporting of all the studies create ambiguity. The overall methodologic quality and reporting of the trials was poor. Between-group analyses, which are necessary to detect a therapeutic effect in controlled clinical trials, were absent from two studies.[31,32] Sample sizes were small, with the exception of two studies,[29,33] and power calculations were absent from all reports. Only one trial was a placebo-controlled and double-blind study,[28] but it was not clear whether this study was randomized. None of the studies scored over 2 points out of 5 on the Jadad score.

Certain aspects of methodology and statistical analysis were inadequately reported in all trials. The statistical values were lacking from all the studies, and few mentioned

whether baseline differences or withdrawals had occurred. None of the studies reported an intent-to-treat analysis. Only two studies mentioned the manufacturer of the CoQ10 used in the trial, and neither identified the actual preparation used (Table 1). Although we aimed to include only monopreparations of CoQ10, we cannot be certain whether emulsifying agents (which can include vitamin E) were present.

Treatment controls varied across and within the trials. Individual differences in patient requirements prevent standardization of the type, dose, and duration of cancer treatments within trials of this nature. These and further variations in types of cancer and outcome measures made it impossible to submit these data to a formal meta-analysis.

Despite this high level of heterogeneity, there were some common features between the studies. In five of six studies, anthracyclines were administered to patients as part of their chemotherapy regimen, and half of the studies measured ECG to assess cardiotoxicity. Between-group analyses revealed significant changes in QRS voltage, QRS duration, QTc duration,[29] and cardiothoracic ratio[30] in the control groups compared with the treatment groups. Thus, CoQ10 may have a stabilizing effect on the heart, but more definite conclusions cannot be drawn to because of insufficient reporting of data.

It was unclear in some studies precisely when the outcome measures were taken. Arrhythmia occurs during administration of anthracycline antibiotics or within several hours of treatment. Disturbances in electrocardioarrhythmia, such as lowered voltage of QRS complex, usually disappear spontaneously within hours or weeks after the completion of chemotherapy.[34] Therefore, the timing of measurements is critical for diagnosing acute toxicity.

There is also controversy over the validity of different monitoring techniques for detecting cardiotoxicity.[24,34,35] It has been suggested that ECG and echocardiography are limited in their ability to detect early reversible cardiac damage or disturbances and that radionuclide angiocardiography provides more accurate measurements of left ventricular function.[34] The transient nature of ECG changes makes detection difficult, requiring 24-hour continuous ECG.[34] However, this was not carried out in any of the trials included in this review.

The effectiveness of the dosages of CoQ10 administered in the studies reviewed here could not be evaluated. Only one study[33] measured and reported pre- and post-treatment plasma levels of CoQ10. A significant increase in serum requires supplementation with approximately 100 mg/d CoQ10,[17] but three studies administered a dose of only 90 mg/d. Optimum levels of CoQ10 have not been determined, and plasma levels are intrinsically variable within a patient. Many factors have been linked with the bioavailability of CoQ10, such as the CoQ10 preparation used, the age, sex, race, diet, and nutritional status of an individual, and the stomach content and alcohol consumption.[36,37] Significantly increased plasma levels of CoQ10 occurred (without supplementation) after treatment with doxorubicin in a recent study.[38] Studies measuring CoQ10 levels before and after courses of anthracycline chemotherapy are lacking.

No adverse effects of CoQ10 were reported in any of the trials. CoQ10 is structurally similar to vitamin K and possesses procoagulant effects. Case reports have suggested that CoQ10 may interact with the anticoagulant effects of warfarin therapy, and concurrent use may cause a diminished response.[39,40] Caution is also advised in selecting a brand of CoQ10 supplement; ConsumerLab (White Plains, NY) reported in January 2004 that one of the 32 products investigated contained no detectable CoQ10 and another exceeded its concentration by 75%.[41]

CoQ10 was not found to interfere with standard treatments in the clinical trials included in this review. It is uncertain whether the cytoprotective and antioxidant activities of CoQ10 may decrease the efficacy of chemotherapeutic agents, such as anthracyclines, which work by inducing oxidative stress. There is no biologic rationale for the selective protection of healthy cells, and interactions between antioxidants and cancer treatments vary according to tumor type and the type and dosages of antioxidant and chemotherapy.[42] A nonsystematic search of preclinical studies revealed conflicting preclinical evidence regarding whether supplementation with CoQ10 benefits or inhibits chemotherapeutic treatments. A preclinical study of doxorubicin concentrations in mice advised caution with concomitant use of CoQ10 and doxorubicin.[43] However, a more recent preclinical study found that CoQ10 treatment had no significant effect on the pharmacokinetics of doxorubicin.[44]

Balancing the benefits and risks of chemotherapy and other cancer treatments is a continuous concern for oncologists and cancer patients and their caregivers. Potential benefits and risks from adjuvant therapies also require careful consideration. Despite encouraging suggestions from clinical trials that CoQ10 might reduce the toxicity of cancer treatments, such effects have not been tested rigorously. There is still much uncertainty over the interactions between CoQ10 and anthracyclines. Further investigations are necessary to determine whether supplementation with CoQ10 is appropriate for improving the tolerability of cancer treatments.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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