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Molecular Replacement for Cancer Metabolic and Mitochondrial Dysfunction, Fatigue and the Adverse Effects of Cancer Therapy

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Abstract. During cancer treatment drug-induced oxidative stress can limit the effectiveness of therapy and cause a number of side effects such as fatigue, nausea, vomiting and diarrhea, as well as more serious adverse effects include cardiomyopathy, peripheral neuropathy, hepatotoxicity, and pulmonary fibrosis. Many of these adverse effects are due to oxidative stress-mediated damage to normal tissues. Antioxidant administration and molecular replacement can mitigate the damage to normal tissues and reduce the adverse effects of cancer therapy without loss of therapeutic potential. For example, loss of efficiency in the electron transport chain caused by membrane peroxidation and reduction in coenzyme Q_{10} can occur during cytotoxic therapy. Molecular replacement of membrane lipids and enzymatic cofactors administered as nutritional supplements with antioxidants can prevent oxidative membrane damage and reductions of cofactors in normal tissues, restore mitochondrial and other cellular functions and reduce the adverse effects of cancer therapy. Recent clinical trials using cancer and non-cancer patients with chronic fatigue have shown the benefit of Molecular Replacement Therapy plus antioxidants in restoring mitochondrial electron transport function, reducing moderate to severe chronic fatigue and protecting mitochondrial and other cellular structures and enzymes from oxidative or other damage due to cytotoxic therapy.

Introduction

Excess cellular oxidative stress (1) is associated with aging and age-related degenerative diseases, and in particular with the etiology of cancer (2-6). Oxidative stress is caused by an excess of reactive oxygen (ROS) and nitrogen (NOS) species over cellular antioxidants, resulting in oxidation of cellular structures, such as membrane lipids and proteins (7, 8) and mutation of DNA (9-11). ROS and NOS are naturally occurring cellular oxidants that are involved in cell proliferation, gene expression, intracellular signaling, antimicrobial defense and other normal cellular processes (12-14), and it is only when ROS/NOS are in excess that cellular damage occurs.

ROS and NOS are normally maintained at appropriate physiological concentrations by cellular antioxidant defenses (15-17). Endogenous cellular antioxidant defenses include the enzymes glutathione peroxidase, catalase, superoxide dismutase, among others (18, 19), and low molecular weight dietary antioxidants (20, 21). These nutritional antioxidants have been used as natural chemopreventive agents (22, 23) to shift the balance of oxidative molecules towards more physiological levels.

The promotion and progression of cancer are linked to excess oxidative stress in many malignancies (24-26). For example, oxidative stress and antioxidant status have been examined in various cancers, such as breast (25-29), renal (30, 31), prostate (32, 33), colorectal (34, 35) and other cancers (36-38). In these studies the oxidative species were in excess of antioxidant properties of the cells, and these cancers were proposed to arise as a consequence of this imbalance and oxidative changes in the genetic apparatus (5, 6, 9-11, 39, 40).

Oxidative stress and cancer chemotherapy

Antineoplastic agents, especially cancer chemotherapy agents, generate ROS/RNS in biological systems (41). Thus, individuals receiving cytotoxic chemotherapy are exposed to excess oxidative stress. The agents that generate high levels of ROS/RNS include: anthracyclines, such as doxorubicin, daunorubicin and epirubicin; alkylating agents; platinum-

coordination complexes, such as cisplatin, carboplatin and oxaliplatin; epipodophyllotoxins, such as etoposide and teniposide; and camptothecins, such as topotecan and irinotecan (41).

The cytochrome P450 monooxygenase system of hepatic microsomes is a primary site of ROS/RNS generation. Enzyme systems such as the xanthine-xanthine oxidase system, and non-enzymatic mechanisms, such as Fenton and Haber-Weiss reactions, also play a role in creating excess oxidative stress during chemotherapy. The anthracyclines generate by far the highest level of oxdative stress of all anti-neoplastic agents. This is due to their ability to displace coenzyme Q_{10} from the electron transport system of cardiac mitochondria (see below), resulting in diversion of electrons directly to molecular oxygen with the formation of superoxide radicals (41).

In contrast to the above noted families of antineoplastic agents, the taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vincristine and vinblastine; anti-metabolites, such as the antifolates; and nucleoside and nucleotide analogues generate only low levels of oxidative stress. Although they do not generate ROS/RNS at tissue sites, such as the hepatic microsomes, they do generate oxidative stress, as do all anti-neoplastic agents, when they induce apoptosis in cancer cells. This is because one of the primary pathways of drug-induced apoptosis is triggered by the release of cytochrome c from the mitochondrial electron transport chain. When this occurs, electrons are diverted from NADH dehydrogenase and reduced coenzyme Q_{10} to oxygen with formation of superoxide radicals.

Drug-induced oxidative stress during cancer chemotherapy not only results in numerous side effects, but it also reduces the anti-cancer efficacy of therapy (41). Antineoplastic agents have clearly established mechanisms of action that do not require or even involve the generation of ROS/RNS (28). However, most chemotherapy drugs can only exert their anti-cancer effects on cancer cells that exhibit unrestricted progression through their cell cycle and have intact apoptotic pathways. Oxidative stress interferes with cell cycle progression by inhibiting the transition of cells from the G_0 (quiescent) to the G_1 phase, slowing progression through the S phase by inhibiting DNA synthesis, blocking cell cycle progression through the restriction point (preventing G_1 to S transition) and causing checkpoint arrest (42-48). These effects of oxidative stress diminish the cytotoxicity of anthracyclines and epipodophyllotoxins that act by inhibiting topoisomerase II activity in the S phase, antifolates and nucleotide/nucleoside analogues that interfere with DNA synthesis in the S phase, vinca alkaloids and taxanes that interfere with the mitotic process primarily during the M phase and camptothecins that inhibit topoisomerase I activity in the S phase. Even platinum coordination complexes and alkylating agents, which are not considered to be phase-specific agents, require cells to progress through the S phase and G_2 phase of the cell cycle in order for apoptosis to occur. Additionally, repair of DNA damage caused by platinum coordination complexes and alkylating agents results in resistance to these drugs, and checkpoint arrest during oxidative stress may enhance the repair processes and diminish the efficacy of the treatment (49-51). In this regard, checkpoint abrogation, the opposite of what occurs during oxidative stress, has been shown to enhance the cytotoxicity of most anti-neoplastic agents. By reducing oxidative stress, antioxidants can counteract the effects of chemotherapy-induced oxidative stress on the cell cycle and enhance the cytotoxicity of anti-neoplastic agents.

In addition to the effects on cell cycle progression, oxidative stress also interferes with drug-induced apoptosis. The two major pathways of drug-induced apoptosis following cellular damage by antineoplastic agents are the mitochondrial pathway, initiated by release of cytochrome c, and the CD95 death receptor pathway, initiated by ligation of the death receptor

by its ligand CD95L (41). The pro-apoptotic signals of CD95 ligation or cytochrome c release activate initiator caspases that subsequently activate effector caspases that carry out disassembly of the cell. Excess oxidative stress during chemotherapy inhibits caspase activity (52-54) and drug-induced apoptosis (55, 56), thereby interfering with the ability of anti-neoplastic agents to kill cancer cells. The aldehydes generated by oxidative stress can also interfere directly with the CD95 pathway by binding to the extracellular domain of the receptor and block CD95L binding.

Cancer associated fatigue and oxidative damage to mitochondrial membranes

Patients undergoing cytotoxic anti-neoplastic therapy frequently complain about the effects of therapy. Fatigue is usually the most common complaint, but other complaints include pain, nausea, vomiting, malaise, diarrhea, headaches, rashes, infections, and other more serious problems can occur, such as cardiomyopathy, peripheral neuropathy, hepatotoxicity, pulmonary fibrosis, mucositis and other effects (28, 57-59). Most cancer patients reported fatigue associated with cancer therapy; however, only one-third of treating physicians recognized this problem (59). Both physicians and patients complained more often of fatigue than pain, and most patients believed that fatigue associated with cancer therapy was untreatable (59).

Cancer patients reported fatigue as a problem before receiving radio- or chemotherapy, but severe fatigue often occurs during or following cancer therapy (58-60). In many studies fatigue was reported as the most troublesome and disabling side effect during cancer therapy (60-63), and it is often a significant reason why patients discontinue treatment (64). Although fatigue is often the most commonly reported adverse symptom during cancer therapy, there has been little effort in controlling or reducing fatigue during therapy of cancer patients (65). Therefore, reducing fatigue associated with cancer therapy is an important goal, and nutritional methods to reduce fatigue and improve the quality of life of cancer patients have been undertaken (66).

Although cancer patients often report fatigue, it is a rather common patient complaint associated with many diseases and disorders. In fact, intractable or chronic fatigue lasting more than six months that is not reversed by sleep is the most common complaint of patients seeking medical care (67-69). It occurs naturally during aging and is also an important secondary condition in many clinical diagnoses (68, 69). The phenomenon of fatigue has been defined as a multidimensional sensation, and recently attempts have been made to determine the extent of fatigue and its possible causes (70, 71). Most patients understand fatigue as a loss of energy and inability to perform even simple tasks without exertion, and many medical conditions are associated with fatigue, including respiratory, coronary, musculoskeletal, and bowel conditions as well as infections and cancer (68-72).

Fatigue is related to reductions in the efficiency of cellular energy systems that are found primarily in mitochondria (66, 72). Damage to mitochondrial components, mainly by oxidation, can impair their ability to produce high-energy molecules, and oxidative stress caused by over-production of ROS/RNS is a major source of mitochondrial damage (2,8,12, 73-75). Important targets of ROS/RNS damage are the phospholipid-containing membranes as well as mitochondrial DNA (73-75), and with aging and disease ROS/RNS damage accumulates and can eventually impair cellular functions (74-77).

During the development of chronic fatigue oxidative damage impairs mitochondrial function. For example, in chronic fatigue syndrome patients there is evidence of oxidative damage to DNA and lipids (80, 81) as well as the presence of oxidized blood markers, such as

methemoglobin, that are indicative of excess oxidative stress (82). Evidence for oxidative damage to DNA and membrane lipids has been found in muscle biopsy samples obtained from chronic fatigue syndrome patients (83). Chronic fatigue syndrome patients have sustained elevated levels of peroxynitrite due to excess nitric oxide, which can result in lipid peroxidation and loss of mitochondrial function as well as changes in cytokine levels that exert a positive feedback on nitric oxide production (84). In addition to mitochondrial membranes, mitochondrial enzymes are also inactivated by peroxynitrite, and this could contribute to loss of mitochrondrial function (85, 86).

Replacement of damaged membrane components by Molecular Replacement Therapy

Mitochondrial targets of ROS/RNS damage are the genetic apparatus and mitochondrial membranes (66, 72-75, 87). In the case of phospholipids in membranes oxidation modifies their structure, and this can affect lipid fluidity, permeability and membrane function (88, 89). One of the most important changes caused by accumulated ROS/RNS damage during aging and in chronic fatigue is loss of electron transport function, and this appears to be directly related to mitochondrial membrane lipid peroxidation (73), which induces permeability changes in mitochondria and loss of transmembrane potential (87).

Lipid Replacement Therapy (66, 72), a form of Molecular Replacement, along with antioxidants have been used to reverse ROS/RNS damage and increase mitochondrial function in certain clinical disorders, such as chronic fatigue and chronic fatigue syndrome (66, 90, 91). Combined with antioxidant supplements, Lipid Replacement Therapy has proven to be an effective method to prevent ROS/RNS-associated changes and can reverse mitochondrial damage and loss of mitochondrial function (90, 91).

Lipid Replacement is possible because cellular lipids are in dynamic equilibrium in the body (72). Orally ingested lipids diffuse to the gut epithelium and are bound and eventually transported into the blood and lymph using specific carrier lipoproteins and also by nonspecific partitioning and diffusion mechanisms (92, 93). Within minutes, lipid molecules are transported from gut epithelial cells to endothelial cells, then excreted into and transported in the circulation bound to lipoproteins and blood cells where they are generally protected from oxidation (93, 94). Once in the blood, specific lipoprotein carriers and red blood cells protect lipids throughout their transport and deposition onto specific cell membrane receptors where they can be taken into cells via endosomes and by diffusion (95). Lipid transporters in the cytoplasm deliver specific lipids to cell organelles where they are taken in by specific transport proteins, partitioning, and diffusion (96). Damaged or oxidized lipids can be removed by a reverse process that is mediated by lipid transfer proteins and enzymes that recognize and degrade damaged lipids (96).

In addition to Lipid Replacement, dietary supplementation with antioxidants and some accessory molecules, such as zinc and certain vitamins, are important in maintaining antioxidant and free-radical scavenging systems (80). There are at least 40 micronutrients required in the human diet (97), and aging increases the need to supplement these to prevent age-associated damage to mitochondria and other cellular elements. Antioxidant use alone, however, may not be sufficient to maintain cellular components free of ROS/RNS damage (98); thus Molecular Replacement is important in replacing ROS/RNS-damaged membrane lipids. During cancer chemotherapy Molecular Replacement is especially important, because excess oxidative stress modifies membranes and mitochondria to an extent far in excess of normal aging and disease (to be discussed below).

Preclinical and clinical studies using Lipid Molecular Replacement/Antioxidant Therapy

Lipid Molecular Replacement Therapy with antioxidants results in replacement of damaged cellular and mitochondrial membrane phospholipids and other lipids that are essential structural and functional components of all biological membranes (72, 73, 87). One such Lipid Molecular Replacement dietary supplement is NTFactor®, and this supplement has been used successfully in animal and clinical lipid replacement studies (91, 98). NTFactor's encapsulated lipids are protected from oxidation in the gut and can be absorbed and transported into tissues without undue damage.

NTFactor has also been used to reduce age-related damage in laboratory animals. In aged rodents, Seidman et al. (98) found that NTFactor prevented hearing loss associated with aging and shifted the threshold hearing from 35-40 dB in control aged animals to 13-17 dB. They also found that NTFactor preserved cochlear mitochondrial function. NTFactor also prevented aging-related mitochondrial DNA deletions found in the cochlear (98). Thus LRT was successful in preventing age-associated hearing loss and reducing mitochondrial damage in rodents.

In clinical studies Lipid Molecular Replacement Therapy has been used to reduce fatigue and protect cellular and mitochondrial membranes from damage by ROS/RNS (90, 91). A vitamin supplement mixture containing NTFactor has been used in a dietary LRT study with severe chronic fatigued patients to reduce their fatigue (99). Using the Piper Fatigue Scale (71) for measurement of fatigue we found that fatigue was reduced approximately 40.5% ($P<0.0001$), from severe to moderate fatigue, after eight weeks of supplementation with NTFactor (99). In more recent studies we examine the effects of NTFactor on fatigue in moderately and mildly fatigued subjects and to determine if their mitochondrial function, as measured by the transport and reduction of Rhodamine-123 and fatigue scores, improved with administration of NTFactor. Oral administration of NTFactor for 12 weeks resulted in a 35.5% reduction in fatigue, respectively ($P<0.001$) (91). In this clinical trial there was good correspondence between reductions in fatigue and gains in mitochondrial function, and after 12 weeks of supplementation, mitochondrial function was found to be similar to that of young healthy adults (91). In contrast, after a 12-week wash-out period fatigue and mitochondrial function were intermediate between the initial starting values and those found after eight or 12 weeks on supplement (91). The results indicate that in moderately to severely fatigued subjects dietary Lipid Molecular Replacement Therapy can significantly improve and even restore mitochondrial function and significantly improve fatigue. Similar findings were observed in chronic fatigue syndrome and fibromyalgia syndrome patients (90).

Lipid Molecular Replacement/Antioxidant Therapy for patients undergoing cancer therapy

Lipid Molecular Replacement Therapy plus antioxidants has also proven useful for reducing adverse effects in patients undergoing cancer chemotherapy. For example, Propax® with NTFactor has been used in cancer patients to reduce some of most common adverse effects of cancer therapy, such as chemotherapy-induced fatigue, nausea, vomiting, malaise, diarrhea, headaches and other side effects (100). Two studies were conducted by Colodny *et al.* (100) on advanced colon, pancreatic or rectal cancers receiving identical 5-FU/methotrexate/Leukovorin

therapy on a 12-week schedule. In the unblinded part of the study the effectiveness of Propax with NTFactor administered before and during chemotherapy was determined by examining the signs/symptoms and side effects of therapy. This quality of life evaluation was conducted by a research nurse, and it was determined that patients on Propax supplementation experienced fewer episodes of fatigue, nausea, diarrhea, constipation, skin changes, insomnia and other effects. In contrast, no changes or a worsening were noted in the occurrence of sore throat or other indications of infection. In the open label part of the trial 81% of patients demonstrated an overall improvement in quality of life parameters while on chemotherapy. In the double-blinded, cross-over, placebo-controlled, randomized part of the study on advanced cancers the patients on Propax Lipid Molecular Replacement Therapy showed improvements in signs/symptoms associated with chemotherapy but only in the arm of the trial where the supplement was administered (100). Lipid Molecular Replacement Therapy with Propax resulted in improvement from fatigue, nausea, diarrhea, impaired taste, constipation, insomnia and other quality of life indicators. Following cross-over from the placebo arm to the supplement arm, 57-70% of patients reported rapid improvements in nausea, impaired taste, tiredness, appetite, sick feeling and other quality of life indicators (100). This preliminary clinical trial demonstrated that usefulness of Lipid Molecular Replacement Therapy and antioxidants given during chemotherapy.

Mechanism of anthracycline-induced mitochondrial damage in cardiac cells

Cancer chemotherapy causes widespread cellular damage (57, 101). For example, anthracycline chemotherapy is associated with dose-related cardiac toxicity that is manifest by acute reversible toxicity (electrocardiographic changes and depressed myocardial contractility) and chronic irreversible cardiomyopathic changes and congestive heart failure. The cellular damage by anthracyclines that is selective for cardiac cells is due to damage and disruption of cardiac mitochondria. The unique sensitivity of cardiac cells to damage by anthracyclines is due a structural component of the electron transport system in cardiac mitochondria that is not present in mitochondria of other tissues and organs (101).

The electron transport system of all mitochondria receives reducing equivalents from NADH dehydrogenase and succinate dehydrogenase that are components of Complex I and Complex II, respectively. These enzymatic components of the complexes face the mitochondrial matrix that is enclosed within the inner mitochondrial membrane. The inner membrane is permeable only to small lipid soluble molecules and substances transferred to the matrix by transport mechanisms. Cardiac mitochondria are unique from mitochondria of other types of cells in that they possess a Complex I-associated NADH dehydrogenase that faces the mitochondrial cytosol (101). Although doxorubicin readily penetrates the outer mitochondrial membrane, due to its hydrophilic properties it cannot penetrate the inner membrane and participate in electron transport chain oxidation-reduction reactions. In cardiac mitochondria, however, doxorubicin interacts with the cytosolic-facing NADH dehydrogenase that is unique to these mitochondria, resulting in reduction of the drug to its semiquinone. Auto-oxidation results in formation of the fully reduced dihydroquinone. This destabilizes the molecule resulting in cleavage of the sugar moiety and formation of doxorubicin aglycones. The aglycones of doxorubicin are highly lipid soluble and readily penetrate the inner membrane where they displace coenzyme Q_{10} (CoQ_{10}) from the electron transport chain. CoQ_{10} normally accepts electrons from Complexes I and II and transfers them down the chain resulting in the formation

of water; however, the aglycones transfer electrons directly to molecular oxygen with the formation of superoxide radicals. Thus doxorubicin generates an exceptionally high level of oxidative stress in cardiac mitochondria, which interferes acutely with cellular energetics and causes acute cardiac toxicity, and it also results in severe damage to mitochondrial DNA.

Damage to the mitochondrial genome by doxorubicin suppresses the regenerative processes of the organelle, including synthesis of electron transport chain components and of mitochondrial ribosomal and transfer RNAs. The inability to synthesize necessary structural components leads to disruption of the mitochondria of cardiac cells and results in myocyte apoptosis. Loss of these contractile cells of the heart results in cardiac insufficiency that does not respond to pharmacological interventions, and may result in cardiac failure and heart transplantation. Fortunately, CoQ_{10} administered during anthracycline therapy reduces or prevents damage to the heart by decreasing anthracycline metabolism within cardiac mitochondria and by competing with anthracycline aglycones for the CoQ_{10} site within the electron transport chain. Thus, CoQ_{10} administered concurrently with anthracyclines maintains the integrity of mitochondrial energetics (101).

Molecular Replacement of CoQ during anthracycline therapy: preclinical studies

Rabbits given intravenous (IV) doxorubicin, 1 mg/kg 3-times weekly every other week for four months (maximum dose: 25 mg/kg) develop severe histological changes in the heart that are characteristic of doxorubicin-induced cardiomyopathy (102, 103). The rabbits also exhibit marked EKG changes and elevation of the creatine phosphokinase level. Three of four rabbits died after cumulative doses of 12, 13, and 19 mg/kg, and only one animal survived a dose of 25 mg/kg. When IV CoQ_{10} (2.5 mg/kg) was administered with each dose of doxorubicin to another group of four rabbits, two died after cumulative doses of 23 and 24 mg/kg doxorubicin, and two survived a cumulative dose of 25 mg/kg. Animals in the CoQ_{10} group exhibited only very minimal histological changes in the heart and minimal EKG changes, suggesting that CoQ_{10} prevented the development of doxorubicin-induced cardiomyopathy (103). In another study the same protocol for doxorubicin and CoQ_{10} administration was used except that CoQ_{10} was not administered until a total of 15 mg/kg of doxorubicin had been given (104). Injections were then continued until a total of 30 mg/kg of doxorubicin was administered. CoQ_{10} administration resulted in improved survival, improvement of the EKG changes observed after the initial 15 mg/kg of doxorubicin, and less histopathological changes in the heart. These findings suggest that CoQ_{10} can prevent the progression of cardiomyopathic changes induced by doxorubicin.

Giving rabbits IV doxorubicin (0.8 mg/kg on three consecutive days each week for three months) resulted in histopathological changes in the heart and changes in EKG (flattened/inverted T waves and decreased QRS voltage) that are characteristic of doxorubicin-induced cardiomyopathy (105). CoQ_{10} (given in IV doses of 0.1 or 0.4 mg/kg 5 days a week beginning with the first doxorubicin injection) significantly reduced the histopathological and EKG changes induced by the drug. These results provide further evidence that CoQ_{10} is cardioprotective during extended therapy with doxorubicin. Chronic administration of doxorubicin (2 mg/kg IP once weekly for 18 weeks) in rats also resulted in histological changes in the heart characteristic of doxorubicin-induced cardiomyopathy (106). As in rabbits, administering CoQ_{10} (10 mg/kg IM 6 days per week) prevented the development of cardiomyopathic changes.

The impact of antioxidants other than CoQ_{10} on the development of chronic doxorubicin-induced cardiotoxicity has been studied in rabbits (107-110) and dogs (111). The antioxidant and antioxidant combinations investigated included vitamin E alone, vitamin E plus sodium selenite, and vitamin E plus vitamin A. The antioxidants were shown to prolong survival of animals by 25-40% (110), but survival was not prolonged in three other experiments (107, 110, 111). Although a modest reduction in the doxorubicin-induced histopathological changes in the heart were reported with some of the antioxidant treatments (107, 109, 110), others (108, 111) observed no protection. Thus, in contrast to the reports that demonstrated prevention of doxorubicin-induced cardiomyopathy by CoQ_{10}, these studies suggest that antioxidant protection alone provides, at best, only minimal protection from the chronic toxicity of anthracyclines.

Molecular Replacement of CoQ_{10} during anthracycline therapy: clinical studies

The impact of CoQ_{10} on the development of doxorubicin-induced cardiotoxicity in lung cancer patients with normal and low cardiac function was investigated by Judy et al. (112). Fourteen adult patients with normal resting cardiac function received 50-70 mg/m^2 of doxorubicin at regular intervals (N=7), or doxorubicin plus 100 mg/day of CoQ_{10} orally beginning 3-5 days before the first dose of doxorubicin and continuing until therapy was completed (N=7). After a total cumulative dose of 600 mg/m^2 doxorubicin, patients not taking CoQ_{10} exhibited marked impairment of cardiac function with a significant increase in heart rate and a substantial decrease in ejection fraction, stroke index, and cardiac index. After a 600 mg/m^2 cumulative dose of doxorubicin in patients receiving CoQ_{10}, cardiac function remained unchanged from that measured before therapy was started. In addition, the seven patients taking CoQ_{10} continued to receive doxorubicin until a total cumulative dose of 900 mg/m^2 was administered, a dose at which approximately 50% of patients treated with doxorubicin can be expected to develop congestive heart failure. Following administration of 900 mg/m^2 of doxorubicin to patients taking CoQ_{10}, the only change in cardiac function was a modest increase in heart rate. Moreover, ejection fraction, stroke index, and cardiac index were unchanged from that measured before therapy was started. The results of this study suggest that CoQ_{10} prevents doxorubicin-induced cardiomyopathy and that it may be possible to escalate the total cumulative dose of doxorubicin when CoQ_{10} is administered concurrently with the drug.

Cortes et al. (113, 114) measured the systolic time interval (STI or pre-ejection period/left ventricular ejection time) in 18 adult patients treated with 50 mg/m^2 doxorubicin (total cumulative dose of 200-500 mg/m^2) plus vincristine and cyclophosphamide every 4 weeks. Eight of ten patients receiving chemotherapy alone exhibited a progressive prolongation of STI (reflecting depressed left ventricular function) with increasing cumulative doses of doxorubicin, and two patients developed congestive heart failure after 200 and 350 mg/m^2 of doxorubicin. In only 2 of 8 patients receiving chemotherapy plus 50 mg/day of PO CoQ_{10} was an increase in STI detected, although one patient did develop congestive heart failure after 350 mg/m^2 of doxorubicin. Although these investigators used only a small dose of CoQ_{10}, the results suggest that CoQ_{10} may prevent the development of doxorubicin-induced cardiotoxicity. Iarussi et al. (115) measured cardiac function in children with hematological malignancies who were treated with equal amounts of doxorubicin and daunorubicin (mean cumulative combined dose: 240 mg/m^2) or the anthracyclines (mean cumulative combined dose: 252 mg/m^2) plus CoQ_{10}, 100 mg

PO twice daily for the duration of the study. Echocardiographic evaluation of ventricular function was performed before therapy, after a total anthracycline dose of 180 mg/m^2, and at the completion of therapy. Left ventricular fractional shortening was reduced in both groups, although it occurred later and to a lesser degree in patients receiving CoQ_{10}. Only patients in the group not receiving CoQ_{10} exhibited depressed interventricular septal wall thickening.

Folkers et al. (116, 117) measured cardiac output in six adult patients with adenocarcinoma of the lung who were treated every 3-4 weeks with doxorubicin (3-5 infusions, total cumulative dose: 250-361 mg), 4 patients receiving 3-4 infusions of doxorubicin (total cumulative dose: 215-355 mg) plus 60 mg/day PO CoQ_{10}, and 5 patients receiving 2 infusions of doxorubicin (total cumulative dose: 145-175 mg) plus 60 mg/day PO CoQ_{10}. All patients receiving doxorubicin without CoQ_{10} exhibited a 25-40% reduction in cardiac output (compared to that before treatment started) following the second (3 patients) or third (3 patients) drug infusion. In patients receiving CoQ_{10}, one exhibited a 16% reduction of cardiac output following the fourth doxorubicin infusion, one exhibited an 18% reduction of cardiac output following the third infusion, and one had a transient reduction of cardiac output following the second infusion but after the third and fourth infusions cardiac output was not significantly different from that measured before treatment started.

Higher doses of CoQ_{10} were even more favorable. Okuma and Ota (118) randomized 80 patients with various types of malignancies to receive doxorubicin or doxorubicin plus CoQ_{10}, 90 mg/day PO beginning one week before chemotherapy was started and continuing until treatment was completed. Patients received 3-10 infusions with a total cumulative doxorubicin dose of 118-517 mg (doxorubicin only group) or 123-517 mg (doxorubicin plus CoQ_{10}). Patients in the doxorubicin only group exhibited myocardial depression with a significant depression of the QRS voltage, beginning with the first infusion, and a significant prolongation of the Q-T interval, starting after the fifth infusion. No significant change in the QRS voltage or the Q-T interval occurred in patients receiving CoQ_{10}.

Results of several other studies also suggest that CoQ_{10} prevented the EKG changes that occur during therapy with doxorubicin. Takimoto et al. (118) investigated the impact of CoQ_{10}, 90 mg/day PO, in a randomized study of 40 patients with lung, breast, and thyroid cancer who were treated with doxorubicin (50 mg/m^2), cyclophosphamide, and 5-fluorouracil plus radiation therapy. They reported that administration of CoQ_{10} reduced the frequency and severity of changes in the QRS complex, S-T segment and T-wave, and the frequency of arrhythmias. Tsubaki et al. (120) reported that IV infusion of 1 mg/kg/day of CoQ_{10}, for four days beginning one day before chemotherapy reduced EKG changes induced by doxorubicin or daunorubicin, and Yamamura (121) reported a similar effect of CoQ_{10}, 30 mg/day PO, in patients being treated with doxorubicin.

Summary

Molecular replacement of lipids and cofactors during cancer chemotherapy reduces the adverse effects of cytotoxic therapy and limits oxidative stress-related damage to normal cellular structures. Such an approach uses oral supplements to replace normal cellular constituents that are damaged as a therapeutic consequence of excess oxidative stress. The use of molecular replacement therapy does not diminish the anti-cancer cell therapeutic properties of chemotherapy drugs. It does, however, help protect normal cells and thus increases the therapeutic ratio of damage to cancer cells versus damage to normal cells. Thus molecular

replacement therapy is a cost-effective and safe method to reduce the adverse effects of cancer chemotherapy.

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