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REVIEW

Reversing mitochondrial dysfunction, fatigue and the adverse effects of chemotherapy of metastatic disease by molecular replacement therapy

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Abstract Metastatic cancers are associated with cellular oxidative stress, and during cancer chemotherapy excess drug-induced oxidative stress can limit therapeutic effectiveness and cause a number of side effects, including fatigue, nausea, vomiting, diarrhea and more serious adverse effects, such as cardiomyopathy, peripheral neuropathy, hepatotoxicity and pulmonary fibrosis. We review here the hypothesis that the acute and chronic adverse effects of cancer chemotherapy can be reduced by molecular replacement of membrane lipids and enzymatic cofactors, such as coenzyme Q_{10}. By administering nutritional supplements with replacement molecules and antioxidants, oxidative membrane damage and reductions of cofactors in normal tissues can be reversed, protecting and restoring mitochondrial and other cellular functions and reducing chemotherapy adverse effects. Recent clinical trials using cancer and non-cancer patients with chronic fatigue have shown the benefit of molecular replacement plus antioxidants in reducing the damage to mitochondrial membranes, restoring mitochondrial electron transport function, reducing fatigue and protecting cellular structures and enzymes from oxidative damage. Molecular replacement and antioxidant administration mitigates the damage to normal tissues, such as cardiac tissue, and reduces the adverse effects of cancer therapy without reduction in therapeutic results.

Keywords Oxidative stress · Alkylating agents · Anthracyclines · Doxorubicin · Mitochondria · Coenzyme Q_{10} · Lipid peroxidation · Electron transport chain · Antioxidants · Membranes

Introduction

Oxidative stress is associated with cancer progression, aging and age-related degenerative diseases [1–3]. It is caused by an excess of reactive oxygen (ROS) and nitrogen (RNS) species over cellular antioxidants, resulting in oxidation of cellular structures, such as membrane lipids and proteins and mutation of mitochondrial and nuclear DNA [4–7]. ROS/RNS are naturally occurring cellular oxidants that are involved in gene expression, intracellular signaling, antimicrobial defense and other normal cellular processes, such as cell proliferation [8–10]. However, when ROS/RNS are in excess cellular damage can occur [4, 8, 10].

Under normal physiological conditions cellular antioxidant defenses maintain ROS/RNS at appropriate concentrations [11–13]. Endogenous cellular antioxidant defenses include the enzymes glutathione peroxidase, catalase, superoxide dismutase, among others [14, 15], and low molecular weight dietary antioxidants [16, 17]. Some of these dietary antioxidants have been used as natural chemopreventive agents to shift the balance of oxidative molecules towards more physiological levels [18, 19].

The promotion and progression of malignant cancers are linked to excess oxidative stress [20–26]. Oxidative stress

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and antioxidant status have been examined in various malignant cancers, such as breast [22–25], renal [26, 27], prostate [28, 29], colorectal [30, 31], among other malignancies [32–34]. In all of these studies ROS/RNS were in excess of antioxidant properties, and thus these cancers were proposed to arise, in part, as a consequence of excess ROS/RNS and oxidative damage to the genetic apparatus [3, 4, 6, 7, 35].

Oxidative stress induced by chemotherapy

Chemotherapeutic agents cause the generation of excess ROS/RNS in biological systems [36, 37]. Thus, individuals receiving cytotoxic chemotherapy are exposed to excess oxidative stress. The highest levels of oxidative stress are generated by anthracycline antibiotics (e.g., doxorubicin, daunorubicin, and epirubicin), although alkylating agents, platinum-coordination complexes (e.g., cisplatin, carboplatin, and oxaliplatin), epipodophyllotoxins (e.g., etoposide and teniposide), and camptothecins (e.g., topotecan and irinotecan) can also produce high levels of ROS/RNS [36, 37].

The primary site of ROS/RNS generation is the cytochrome P450 monooxygenase system of hepatic microsomes [36, 38]. 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 very high levels of oxidative stress generated by anthracyclines is due to their ability to displace coenzyme Q_{10} (CoQ_{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 [36–38].

Some cancer chemotherapeutic agents generate only modest amounts of ROS/RNS. In contrast to the anthracycline antibiotics, platinum-coordination complexes and camptothecins, the taxanes (e.g., paclitaxel and docetaxel), vinca alkaloids (e.g., vincristine and vinblastine), antimetabolites, such as the antifolates, and nucleoside and nucleotide analogues generate only low levels of oxidative stress [36–38]. They do, however, generate some oxidative stress, as do all antineoplastic agents, when they induce apoptosis in cancer cells. This occurs when 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 CoQ_{10} to oxygen, resulting in the formation of superoxide radicals [39].

During cancer chemotherapy drug-induced oxidative stress produces side effects and reduces the anticancer efficacy of therapy [36]. Antineoplastic agents have clearly established mechanisms of action that do not depend upon the generation of ROS/RNS [38]. However, the drugs only exert their anticancer 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 inhibition of DNA synthesis, inhibiting cell cycle progression through the restriction point (preventing G_1 phase to S phase transition), and by causing checkpoint arrest [40–46].

Thus the effects of oxidative stress diminish the cytotoxicity of anthracyclines and epipodophyllotoxins that act in the S phase and inhibit topoisomerase II activity as well as antifolates and nucleotide/nucleoside analogues that also act in the S phase and interfere with DNA synthesis. In contrast, vinca alkaloids and taxanes act primarily during the M phase and interfere with the mitotic process, whereas camptothecins act in the S phase and inhibit topoisomerase I activity. Platinum coordination complexes and alkylating agents, which are not considered to be phase-specific agents, still require cells to progress through the S phase and G_2 phase of the cell cycle in order for apoptosis to occur [44, 45].

DNA repair of damage caused by alkylating agents and platinum coordination complexes results in resistance to these drugs, and checkpoint arrest during oxidative stress can enhance the repair processes and diminish the efficacy of the treatment [47–49]. Interestingly, checkpoint abrogation–the opposite of what occurs during oxidative stress–enhances the cytotoxicity of antineoplastic agents. By reducing oxidative stress, antioxidants counteract the effects of chemotherapy-induced oxidative stress on the cell cycle and enhance the cytotoxicity of antineoplastic agents [36].

Oxidative stress also interferes with drug-induced apoptosis, important intracellular signal transduction pathways that are necessary for some antineoplastic agents [50] to exert their cytotoxic effect on cancer cells. 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 binding to the death receptor of its ligand CD95L [48]. The proapoptotic signals of CD95 ligation or cytochrome c release activate initiator caspases that subsequently activate effector caspases that carry out disassembly of the cell. Oxidative stress during chemotherapy results in the generation of highly electrophilic aldehydes that have the ability to bind to the nucleophilic active sites of caspases as well as the nucleophilic extracellular domain of the CD95 death receptor. This inhibits caspase activity and the binding of CD96L ligand, thus interfering with the ability of antineoplastic agents to initiate apoptotic cell death [50–54].

Mitochondrial damage induced by anthracyclines

Cardiac mitochondria are especially sensitive to chemotherapy with anthracycline antibiotics [55]. Anthracycline-induced cardiac toxicity is characterized by acute, reversible toxicity that causes electrocardiographic changes and depressed myocardial contractility and by chronic, irreversible, dose-related cardiomyopathy [reviewed in 36]. The selective toxicity to cardiac cells that is caused by anthracyclines is due to disruption and damage 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. Specifically, cardiac mitochondria are unique from mitochondria of other cell types in that they possess a Complex I-associated NADH dehydrogenase that faces the mitochondrial cytosol [56, 57].

Anthracyclines like doxorubicin possess a hexose sugar (daunosamine) attached to a tetracycline structure containing adjacent quinone and hydroquinone moieties that permit this class of drug to participate in oxidation–reduction reactions. Due to its small molecular weight (580 d) doxorubicin readily penetrates the outer mitochondrial membrane, but because of its hydrophilic properties it cannot penetrate the inner membrane. Thus, it cannot participate in oxidation-reduction reactions with the matrix-facing dehydrogenases of the electron transport chain found in most types of cells, such as liver, kidney and tumor cells [56–58]. In cardiac cells, however, doxorubicin interacts with the cytosolic-facing NADH dehydrogenase that is unique to cardiac mitochondria, resulting in reduction of the drug to its semiquinone [59–62]. The semiquinone is then auto-oxidized to the fully reduced dihydroquinone, and this reaction destabilizes the molecule resulting in cleavage of the sugar moiety and formation of doxorubicin aglycones [62].

The aglycones of doxorubicin are highly lipid soluble and readily penetrate the inner mitochondrial membrane where they displace CoQ_{10} from the electron transport chain. Thus when doxorubicin is administered in vivo, there is an increase in the plasma concentration of CoQ_{10} [63] and a decrease in the content of CoQ_{10} in cardiac muscle [64]. Once doxorubicin aglycones displace CoQ_{10} from the mitochondrial inner membrane, they serve as electron acceptors from Complex I and Complex II. 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 the electrons directly to molecular oxygen leading to the formation of superoxide radicals [62]. Therefore, doxorubicin generates an exceptionally high level of oxidative stress in cardiac mitochondria, interfering with cellular energetics (acute cardiac toxicity) and also resulting in severe damage to mitochondrial DNA [65, 66].

Anthracycline damage to mitochondrial DNA blocks the synthesis of mitochondrial ribosomal and transfer RNA that are necessary for the regenerative processes of the mitochondria, including the synthesis of electron transport chain components [67]. The inability of anthracycline-damaged mitochondria to sustain their structure and function results in disruption of cardiac cell mitochondria, resulting in cardiomyocyte apoptosis. Loss of these contractile cells of the heart causes cardiac insufficiency that does not respond to pharmacological interventions. Ultimately this may result in cardiac failure requiring the patient to undergo a heart transplantation. However, if CoQ_{10} is administered during chemotherapy with anthracyclines, it 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, it has been hypothesized that CoQ_{10} administered concurrently with anthracyclines maintains the integrity of cardiac mitochondria and prevents damage to the heart while also enhancing the anti-cancer activity of the anthracyclines by diminishing their catabolism.

Molecular replacement of CoQ_{10} during anthracycline chemotherapy: preclinical data

Molecular replacement of CoQ_{10} dramatically prevents development of anthracycline-induced cardiomyopathy and histopathological changes in animal studies. For example, rabbits given IV doxorubicin at a dose of 1 mg/kg 3 times weekly every other week for a total of 4 months develop severe histological changes in heart tissue that are characteristic of doxorubicin-induced cardiomyopathy. The rabbits also showed marked EKG changes and elevations in the level of creatine phosphokinase [68]. When 2.5 mg/kg CoQ_{10} was administered IV with each dose of doxorubicin to another group of rabbits, the animals developed only very minimal histological changes in the heart and exhibited only minimal changes in their EKG patterns. The same protocol for doxorubicin and CoQ_{10} administration was used in another study, except that CoQ_{10} was not administered until a total of 15 mg/kg of doxorubicin had been given. Injections IV were then continued until a total of 30 mg/kg of doxorubicin was administered. The administration of CoQ_{10} resulted in increased survival, improvement in the EKG patterns observed after the initial 15 mg/kg of doxorubicin, and reduced histopathological changes in the heart [69]. These findings indicate that CoQ_{10} administration during chemotherapy can prevent the cardiomyopathic changes induced by doxorubicin.

Further evidence for a cardioprotective effect of CoQ10 during doxorubicin therapy was seen in a longer study. Rabbits were given doxorubicin IV (0.8 mg/kg) on 3 consecutive days each week for 3 months [70]. The treatment resulted in histopathological changes in the heart and EKG changes (flattened/inverted T waves and decreased QRS voltage) that are characteristic of doxorubicin-induced cardiomyopathy [74]. CoQ (at doses of 0.1 or 0.4 mg/kg) given IV 5 days a week beginning with the first doxorubicin injection significantly reduced the histopathological and EKG changes induced by the drug.

Using rats chronic administration of doxorubicin IP (2 mg/kg once weekly for 18 weeks) resulted in histological changes of the heart that are characteristic of doxorubicin-induced cardiomyopathy [71]. As in rabbits, the administration of CoQ_{10} (10 mg/kg IM 6 days per week) to rats prevented the development of cardiomyopathic changes in the doxorubicin-treated animals [71].

The above preclinical data support the contention that CoQ_{10} protects the heart from anthracycline-induced cardiotoxicity. However, the impact of CoQ_{10} on the antineoplastic efficacy of anthracyclines has not been studied.

Molecular replacement of CoQ_{10} during anthracycline chemotherapy: clinical data

The concurrent administration of CoQ_{10} during chemotherapy can affect both acute and chronic cardiotoxicity caused by anthracyclines. For example, the importance of administering CoQ_{10} on the development of doxorubicin-induced cardiotoxicity in patients with lung cancer was investigated by Judy et al. [72]. Fourteen adult patients with normal resting cardiac function received 50–70 mg/m^2 IV of doxorubicin at regular intervals, or doxorubicin plus 100 mg/day of CoQ_{10} PO, beginning 3–5 days before the first dose of doxorubicin and continuing until therapy was complete. After a total cumulative dose of 600 mg/m^2 doxorubicin, the patients receiving doxorubicin alone 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. However, in patients receiving 600 mg/m^2 of doxorubicin IV along with CoQ_{10} PO, cardiac function remained unchanged from that measured before therapy was started. Additionally, the patients taking CoQ_{10} continued to receive doxorubicin until they received a total of 900 mg/m^2, a dose at which approximately 50% of patients treated with doxorubicin alone can be expected to develop cardiomyopathy with congestive heart failure [55]. Following administration of 900 mg/m^2 in those patients taking CoQ, the only change in cardiac function was a modest increase in heart rate, whereas ejection fraction, stroke index and cardiac index were unchanged from that measured before therapy was started. This study demonstrated that CoQ_{10} prevents doxorubicin-induced cardiomyopathy and that the total cumulative dose of doxorubicin can be escalated when CoQ_{10} is administered concurrently with the chemotherapeutic drug.

Other studies confirm the results of Judy et al. [72]. For example, Cortes et al. [73, 77, 78] measured systolic time intervals (the 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 the 10 patients receiving chemotherapy alone exhibited a progressive prolongation of their systolic time intervals, indicating depressed left ventricular cardiac function, with increasing cumulative doses of doxorubicin, while two patients developed congestive heart failure after 200 and 350 mg/m^2 of doxorubicin. Only 2 of 8 patients receiving chemotherapy plus 50 mg/day of oral CoQ_{10} showed an increase in systolic time interval, although one patient developed heart failure after 350 mg/m^2 of doxorubicin. Although these investigators used only small doses of CoQ_{10}, the results indicated that CoQ_{10} can reduce the cardiac toxicity of doxorubicin.

Cardiac protection has also been seen in children treated with anthracyclines plus oral CoQ_{10}. Iarussi et al. [79] 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 with anthracyclines (mean cumulative combined dose: 252 mg/m^2) plus 100 mg of oral CoQ_{10} twice daily for the duration of the study. Cardiac function was evaluated by echocardiographic evaluation before therapy started, after a cumulative anthracycline dose of 180 mg/m^2 and at the completion of therapy. They found that left ventricular function was reduced in both groups (10 children in each group), although it occurred later and to a lesser degree in patients receiving oral CoQ_{10} [75].

Investigators have seen consistent differences in cardiac output between patients who received oral CoQ_{10} during anthracycline therapy and those that did not. For example, Folkers et al. [75] measured cardiac output before and during treatment of 6 adults with lung cancer receiving doxorubicin every 3–4 weeks (3–5 infusions, total cumulative dose of 250–361 mg), or 4 patients receiving doxorubicin (total cumulative dose of 215–355 mg) plus 60 mg/day oral CoQ_{10}, or two infusions of doxorubicin (total cumulative dose of 145–175 mg) plus 60 mg/day oral CoQ_{10}. The patients who received doxorubicin without CoQ_{10} showed a 25–40% reduction in cardiac output following the second or third drug infusion. However, 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 that resolved. The remaining patients showed no change in cardiac output during treatment. Thus the majority of patients in these studies maintained their cardiac output when CoQ_{10} was added during chemotherapy treatment [75].

In addition to cardiac output, changes in EKG profiles have been seen during anthracycline therapy that are prevented by oral CoQ_{10}. Okuma and Ota [76] randomized 80 cancer patients to receive doxorubicin (total cumulative dose 118–517 mg) or doxorubicin (total cumulative dose 123–517 mg) plus oral CoQ_{10} (90 mg/day). Patients receiving doxorubicin alone had significant myocardial depression of the QRS voltage beginning with the first infusion and a significant prolongation of the Q-T interval after the fifth infusion. However, significant changes in the QRS voltage or the Q-T interval did not occur in patients receiving doxorubicin plus CoQ_{10}. Takimoto et al. [77] investigated the impact of oral CoQ_{10} (90 mg/day) in a randomized study of 40 cancer patients who were treated with doxorubicin (50 mg/m^2), cyclophosphamide, 5-fluorouracil plus radiation therapy. They found 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.

Although limited in number, the above clinical studies support the preclinical data that suggest that CoQ_{10} protects the heart from the cardiotoxicity of anthracyclines. However, like preclinical studies, the impact of CoQ_{10} on the antineoplastic efficacy of anthracycline-based chemotherapy has not been studied.

Cancer fatigue, aging and oxidative damage to mitochondria

Fatigue is usually the most common complaint of cancer patients undergoing therapy, but other complaints include pain, nausea, vomiting, malaise, diarrhea, headaches, rashes and infections. Other more serious problems can also occur, such as cardiomyopathy, peripheral neuropathy, hepatotoxicity, pulmonary fibrosis, mucositis and other effects [78, 79]. Interestingly, most patients felt that cancer theapy-associated fatigue was untreatable [80]. Although fatigue is often the most commonly reported adverse symptom during cancer therapy, there has been little effort directed at reducing fatigue [81]. Therefore, reducing fatigue associated with cancer therapy is an important goal, and nutritional methods have been undertaken to reduce fatigue and improve the quality of life of cancer patients [82]. Although fatigue in cancer patients has been defined as a multidimensional sensation [83], most patients understand fatigue as a loss of energy and inability to perform even simple tasks without exertion [83, 84].

At the tissue level fatigue is related to reductions in the efficiency of cellular energy systems in mitochondria [82, 85]. Damage to mitochondrial components, mainly by oxidation, can impair mitochondrial function, resulting in oxidative stress caused by over-production of ROS/RNS [reviews: 1, 5, 8]. Mitochondrial membranes and DNA are major targets of oxidative stress, and with aging ROS/RNS mitochondrial damage accumulates [86, 87].

In addition to aging, oxidative damage impairs mitochondrial function resulting in chronic fatigue. For example, in chronic fatigue syndrome (CFS) patients there is evidence of oxidative damage to DNA and lipids [88, 89] as well as oxidized blood markers [90] and muscle membrane lipids [91] that are indicative of excess oxidative stress [90]. CFS patients also 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 [92].

Molecular replacement of oxidized membrane components

Membranes are especially sensitive to oxidative damage by ROS/RNS. Membrane phospholipid oxidation modifies their structure, affecting lipid fluidity, permeability and membrane function [93, 94]. One of the most important changes caused by ROS/RNS damage is loss of electron transport function, and this appears to be directly related to mitochondrial membrane lipid peroxidation, which induces permeability changes in mitochondria and loss of transmembrane potential, an essential requirement of mitochondrial oxidative phosphorylation [95, 96].

Lipid Replacement Therapy [82, 85] plus antioxidants has been used to reverse ROS/RNS damage and increase mitochondrial function in certain clinical disorders, such as chronic fatigue, CFS and Fibromyalgia Syndrome [82, 97]. Lipid Replacement Therapy has has been found to be effective in preventing ROS/RNS-associated changes and reversing mitochondrial damage and loss of function [97, 98].

Molecular/lipid replacement therapy: preclinical and clinical data

Oral molecular/lipid replacement therapy with unoxidized lipids and antioxidants has been effective in replacement of damaged cellular and mitochondrial membrane

phospholipids and other lipids that are essential structural and functional components of all biological membranes [98, 99]. NTFactor®, a Lipid Replacement oral supplement containing phospholipids, phosphoglycolipids, cardiolipids and other membrane lipids, has been used successfully in animal and clinical lipid replacement studies [97–100]. NTFactor's encapsulated lipids are protected from oxidation in the gut and can be absorbed and transported into tissues without oxidation.

In preclinical studies NTFactor has been used to reduce age-related damage in rodents. Seidman et al. [100] 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 [100]. Thus NTFactor was successful in preventing age-associated hearing loss and reducing mitochondrial damage in rodents.

In clinical studies molecular/lipid replacement therapy has been used to reduce fatigue and protect cellular and mitochondrial membranes from damage by ROS/RNS [97–99]. A vitamin supplement mixture containing NTFactor was by used by Ellithorpe et al. [99] in a dietary molecular replacement study of 34 patients with severe chronic fatigued patients to reduce their fatigue by approximately 40.5% in 8 weeks. In these studies fatigue was monitored by use of the Piper Fatigue Scale to measure clinical fatigue and quality of life [83]. In addition, in a subsequent study we examined the effects of NTFactor on fatigue and mitochondrial function in 20 patients [98]. Oral administration of NTFactor for 12 weeks resulted in a 35.5% reduction in fatigue [98]. 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. In contrast, after a 12-week wash-out period fatigue increased and mitochondrial function decreased [98]. Thus in fatigued subjects dietary molecular/lipid replacement therapy can significantly improve and even restore mitochondrial function and significantly improve fatigue. Similar findings were observed in CFS and Fibromyalgia Syndrome patients [97].

Molecular/lipid replacement therapy during cancer chemotherapy

Molecular/lipid molecular replacement therapy plus antioxidants has been used for reducing the adverse effects of chemotherapy in cancer patients. For example, Propax (a vitamin–mineral mixture 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 [101]. In two studies conducted by Colodny et al. [101] on 38 advanced metastatic colon, pancreatic or rectal cancer patients receiving 5-FU/methotrexate/Leukovorin therapy on a 12-week schedule molecular/lipid replacement was used to reduce adverse therapy effects. In the first 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. A quality of life evaluation was conducted by a research nurse, and it was determined that patients on NTFactor supplementation experienced significantly 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 this open label trial 81% of patients demonstrated an overall improvement in quality of life parameters while on chemotherapy [101]. In the double-blinded, cross-over, placebo-controlled, randomized part of the study on advanced cancers the patients on molecular/lipid molecular replacement therapy showed improvements in signs/symptoms associated with the adverse effects of chemotherapy [101]. Molecular/lipid molecular replacement therapy resulted in improvements in incidence of 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 [101]. This clinical trial clearly demonstrated the usefulness of molecular/lipid molecular replacement therapy and antioxidants given during chemotherapy.

Summary

Oral molecular replacement therapy during cancer chemotherapy of metastatic disease can significantly reduce the adverse effects of cytotoxic drugs and limit the oxidative stress-related damage to normal cellular structures. Molecular replacement supplements can be used to replace normal cellular constituents that are damaged as a therapeutic consequence of excess oxidative stress as well as those damaged due to aging and chronic disease. Molecular replacement therapy does not modify the anti-cancer cell therapeutic properties of chemotherapy drugs, but it does help protect normal cells and thus increases cancer therapeutic ratio. We conclude that molecular replacement therapy is a cost-effective and safe method to reduce the adverse chronic and acute effects of cancer chemotherapy and improve clinical outcome [37].

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