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Lipid Replacement Therapy: a nutraceutical approach for reducing cancer-associated fatigue and the adverse effects of cancer therapy while restoring mitochondrial function

Garth L. Nicolson*

The Institute for Molecular Medicine, Huntington Beach, CA 92647, USA,

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Correspondence: Prof. Garth L. Nicolson, Department of Molecular Pathology, The Institute for Molecular Medicine, P.O. Box 9355, S. Laguna Beach, California 92652, Tel: +1-949-715-5978, Email: gnicolson@immed.org, Website: www.immed.org.

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Running Title: Cancer-Associated Fatigue and Mitochondria

Abstract Cancer-associated fatigue is one of the most common symptoms in all forms and stages of cancer, yet scant attention is usually given to patients who have symptomatic complaints of fatigue. Cancer-associated fatigue is also associated with cellular oxidative stress, and during cancer therapy excess drug-induced oxidative stress can limit therapeutic effectiveness and cause a number of side effects, including fatigue, nausea, vomiting and more serious adverse effects. Cancer-associated fatigue and the chronic adverse effects of cancer therapy can be reduced by Lipid Replacement Therapy using membrane lipids along with antioxidants and enzymatic cofactors, such as coenzyme Q_{10}, given as food supplements. Administering these nutraceutical supplements can reduce oxidative membrane damage and restore mitochondrial and other cellular functions. Recent clinical trials using cancer and non-cancer patients with chronic fatigue have shown the benefits of Lipid Replacement Therapy in reducing fatigue and restoring mitochondrial electron transport function.

1 Introduction—Cancer-associated fatigue

Cancer-associated fatigue is a pervasive problem that adds considerably to morbidity and exists in all types of cancers from the earliest to most progressed forms [1, 2]. Along with pain and nausea, it is one of the most common and disabling symptoms of cancer [1-3], especially in advanced cancers [3-5]. The prevalence of cancer-associated fatigue is reported to be as high as 95% in patients receiving adjuvant therapies [6]. It is a problem before, during and after therapy and can continue to be a problem years after treatment has ended [1, 4]. Since it has such a negative effect on the impact and quality of life, addressing and reducing cancer-associated fatigue is an important aspect of the treatment of cancer, especially treatment of metastatic cancers.

Cancer-associated fatigue is not well understood, but it is thought to be a combination of the effects of the cancer itself plus the effects of cancer treatments [1, 2, 4]. Up until recently cancer-associated fatigue was rarely treated and thought to be an unavoidable symptom [1, 2]. More recently, however, there have been discussions on how to increase our efforts in understanding and treating cancer-associated fatigue as well as ways to distinguish between depression and cancer-associated fatigue [2]. Both depression and fatigue have multidimensional and heterogeneous qualities, with physical, cognitive and emotional

dimensions and a certain degree of overlap across these dimensions [2]. Since fatigue or loss of energy is a core aspect of diagnosing depression, both fatigue and depression are often diagnosed together in cancer patients, usually by self assessment, and they are considered to be part of a clinical symptom cluster, co-morbitity or syndrome [7, 8]. However, there are techniques that can distinguish between these two symptoms by removal of fatigue-associated assessments from analysis of depression [9, 10]. Also, when assessing fatigue, criteria have been established that take depression into consideration, and these symptoms can be separated out by considering aspects that are not shared between the two symptoms [11].

Cancer-associated fatigue is now thought to be the product of a variety of contributing factors [12]. In addition to a decrease in the availability of cellular energy and as mentioned above, depression, there are other psychological factors (anxiety, sleep disturbances, among others) as well as anemia, endocrine changes, poor nutritional status, release of inflammatory cytokines and cancer therapy [6, 13, 14]. Cancer-associated fatigue does not occur as an isolated symptom—it occurs among multiple symptoms and is well correlated with decreased functional status [15].

The most commonly found, troublesome and disabling effect of cancer therapy is fatigue [6, 14-16]. Fatigue can vary in degree from mild to severe during cancer therapy, and it is often a significant reason why patients discontinue therapy [17]. Reviewing articles on the effects of cancer therapy on fatigue Manzullo and Escalante [14] noted that 80-96% of patients receiving chemotherapy and 60-93% receiving radiotherapy experienced moderate to severe fatigue, and fatigue continued for months—or even years—after cancer therapy ended. Thus controlling cancer-associated fatigue as well as fatigue caused by cancer treatment are important goals [18]. This review will concentrate on cancer-associated and non-cancer-associated fatigue and the nutritional approaches used to reduce and control fatigue.

2 Chronic fatigue, oxidative stress and damage to mitochondrial membranes

Chronic fatigue or intractable fatigue lasting more than 6 months that is not reversed by normal sleep is the most common complaint of patients seeking general medical care [19, 20]. It occurs naturally during aging and is also an important secondary condition in many clinical diagnoses [20, 21]. Most fatigued patients understand fatigue as a loss of energy and inability to perform

even simple tasks without exertion. Many medical conditions are associated with fatigue, including respiratory, coronary, musculoskeletal, and bowel conditions as well as infections [19-21]. However, this symptom is especially apparent in overwhelming majority of cancer patients [1, 4, 6, 12].

Another phenomenon associated with cancer and its progression, aging and age-related degenerative diseases is oxidative stress [22-24]. Oxidative stress is caused by an intracellular excess of reactive oxygen (ROS) and nitrogen (RNS) free radical species over intracellular antioxidants. When this imbalance occurs, it results in oxidation of cellular structures, such as membrane lipids and proteins, and mutation of mitochondrial and nuclear DNA [25-28]. ROS/RNS are naturally occurring cellular free radical oxidants that in low concentrations are involved in gene expression, intracellular signaling, antimicrobial defense and other normal cellular processes, such as cell proliferation [29-31]. However, when ROS/RNS are in great excess over antioxidants, cellular damage can occur [25, 29, 31]. Recently a link between excess oxidative stress and activation of ROS/RNS pathways with fatigue and fatiguing illnesses has been proposed by Maes [32, 33].

In non-symptomatic subjects under normal physiological conditions cellular antioxidant defenses maintain ROS/RNS at appropriate concentrations that prevent excess oxidation of cellular structures [34-36]. Endogenous cellular antioxidant defenses include the enzymes glutathione peroxidase, catalase, superoxide dismutase, among others [37, 38], and low molecular weight dietary antioxidants [39, 40]. Some of these dietary antioxidants have been used as natural chemopreventive agents to shift the excess concentrations of oxidative molecules towards more physiological levels [41, 42].

The promotion and progression of malignant cancers are linked to excess oxidative stress and primarily its mediators, excess ROS/RNS [43-47]. Oxidative stress and antioxidant status have been examined in various malignant cancers, such as breast [44, 45, 47, 48], prostate [49, 50], colorectal [51, 52], renal [53, 54], and other malignancies [55-57]. In all of these studies ROS/RNS, and thus oxidative stress, were in excess of antioxidant concentrations. Thus these cancers could have been induced as a consequence of excess ROS/RNS and oxidative damage to the genetic apparatus [24, 25, 28, 58].

3 Oxidative stress and fatigue induced by cancer therapy

Anti-cancer therapy, such as chemotherapy, can result in the generation of excess ROS/RNS and thus excess oxidative stress that can damage biological systems [59, 60]. During chemotherapy the highest known levels of oxidative stress are generated by anthracycline antibiotics, followed (in no particular order) by alkylating agents, platinum-coordination complexes, epipodophyllotoxins, and camptothecins [59, 60]. The primary site of ROS/RNS generation during cancer chemotherapy is the cytochrome P450 monooxygenase system within liver microsomes [59, 61]. Enzyme systems such as the xanthine-xanthine oxidase system, and non-enzymatic mechanisms (Fenton and Haber-Weiss reactions) also play a role in creating excess oxidative stress during chemotherapy. The very high levels of oxidative stress caused by anthracyclines is related to their ability to displace coenzyme Q_{10} (CoQ_{10}) from the electron transport system of cardiac mitochondria, resulting in diversion of electrons directly to molecular oxygen with the formation of superoxide radicals [59-61].

Not all chemotherapeutic agents generate oxidative stress and high levels of ROS/RNS. Some agents generate only modest amounts of ROS/RNS. Examples of the latter are: platinum-coordination complexes and camptothecins, taxanes, vinca alkaloids, anti-metabolites, such as the antifolates, and nucleoside and nucleotide analogues [59-61]. All of these agents do, however, generate some oxidative stress, as do all antineoplastic agents, when they induce apoptosis in cancer cells. 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 [61, 62].

Treatment of cancer using chemotherapeutic agents causes oxidative stress and produces side effects, including fatigue, that reduce the efficacy of therapy [59-61]. Antineoplastic agents have clearly established mechanisms of action that do not depend upon the generation of ROS/RNS [60, 61]. However, these drugs can only mediate 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 to G_1 phase, slowing progression through S phase by inhibition of DNA synthesis, inhibiting cell cycle progression of G_1 to S phase, and by checkpoint arrest [63-67].

Cells react to chemotherapeutic agents by increasing or activating their DNA repair systems [68-70]. DNA repair of damage caused by alkylating agents and platinum complexes

results in resistance to these drugs, and checkpoint arrest during oxidative stress can enhance the repair processes and diminish the efficacy of treatment [68-70]. Abolishing checkpoint arrest produces the opposite effect and 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 [59].

Oxidative stress can interfere with chemotherapy-induced apoptosis, and oxidative stress can affect important intracellular signal transduction pathways that are necessary for the action of some antineoplastic agents [59, 71, 72]. 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 CD95L binding to its death receptor [69]. 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 extracellular domain of the CD95 death receptor. This inhibits caspase activity and the binding of CD96L ligand, impairing the ability of antineoplastic agents to initiate apoptosis [59, 72-74].

Radiotherapy also results in generation of oxidative stress and ROS/RNS [75, 76]. The principal target of radiation is tumor cell DNA, and tumor cell DNA can be damaged directly by radiation, but genetic damage is also mediated by ROS/RNS [76, 77]. Recently the principal source of ROS/RNS during radiotherapy has been shown to be the mitochondria [77, 78]. The initial cytotoxicity of radiation is now thought to be due to ROS/RNS triggering of apoptosis by altering mitochondrial metabolism, transiently opening mitochondrial permeability transition pores and increasing the influx of calcium ions into the matrix, thus stimulating mitochondrial nitric oxide synthase and generating nitric oxide, which inhibits the respiratory chain and eventually stimulates ROS/RNS free radicals that initiate apoptosis [78, 79].

4 Mitochondrial damage induced by cancer therapy

One of the most difficult side effects of cancer chemotherapy is caused by drug damage to mitochondria [60, 61]. Cardiac mitochondria are especially sensitive to certain chemotherapy agents, such as anthracycline antibiotics [80]. 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 [59, 80]. The selective anthracycline-induced toxicity to cardiac cells is due to damage of cardiac mitochondria. The sensitivity of cardiac cells to anthracyclines, such as doxorubicin, has been found to be due to the unique properties of cardiac mitochondria in that they possess a Complex I-associated NADH dehydrogenase that faces the mitochondrial cytosol [81, 82].

Due to its small molecular weight doxorubicin readily penetrates the outer mitochondrial membrane, but because of its hydrophilic properties it cannot penetrate the inner membrane [80, 83]. Thus, it cannot participate in oxidation-reduction reactions with the type of matrix-facing dehydrogenases of the electron transport chain found in most types of cells, including most tumor cells [80, 83]. In cardiac cells doxorubicin interacts with the mitochondrial cytosolic-facing NADH dehydrogenase that is unique to this tissue [84, 85]. This interaction produces doxorubicin aglycones [86], which are highly lipid soluble and readily penetrate the inner mitochondrial membrane where they displace CoQ_{10} from the electron transport chain [80, 84]. Thus during doxorubicin treatment the plasma concentration of CoQ_{10} [87] increases while CoQ_{10} in cardiac muscle decreases [88]. 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 [91]. Thus, doxorubicin generates a high level of oxidative stress in cardiac mitochondria, causing acute cardiac toxicity and damage to mitochondrial DNA [80, 85, 89].

The inability of anthracycline-damaged cardiac cell mitochondria to sustain their function and structure results in disruption of mitochondria and apoptosis [80, 86]. This produces cardiac insufficiency that does not respond to pharmacological interventions and ultimately cardiac failure. 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 aglycones for the CoQ_{10} site within the electron transport chain [80]. Thus, CoQ_{10} administered concurrently with anthracyclines can maintain the integrity of cardiac mitochondria and prevent damage to the heart while enhancing the anti-cancer activity of anthracyclines [61, 80].

Radiotherapy also produces damage to tissues other than cancerous tissues, and agents that protect tissues against radiation effects have been used to reduce unwanted damage [78, 92]. The types of radioprotective agents that have been used to decrease the adverse effects of

radiotherapy are: antioxidants, free radical scavengers, inhibitors of nitric oxide synthase and anti-inflammatory and immunomodulatory agents [78, 92]. The most effective of these under development target the mitochondria, such as proteins and peptides that can be transported into mitochondria and plasmids or nucleotide sequences, for example, that target and stimulate mitochondrial manganese superoxide dismutase genes to produce this important dismutase [78].

5 Replacement of mitochondrial cofactors during chemotherapy

Chemotherapy can displace important mitochondrial cofactors, such as CoQ_{10} [80]. During chemotherapy replacement of CoQ_{10} dramatically prevents development of anthracycline-induced cardiomyopathy and histopathological changes in animals. It can also prevent changes in electrocardiograms (EKG) characteristic of anthracycline-induced damage [93]. The administration of CoQ_{10} resulted in increased survival, improvement in the EKG patterns, and reduced heart histopathological changes [94]. These preclinical data (and additional data discussed in [59, 60, 80]) support the contention that CoQ_{10} protects the heart from anthracycline-induced cardiotoxicity.

In patients concurrent administration of CoQ_{10} during chemotherapy can affect both acute and chronic cardiotoxicity caused by anthracyclines [59, 60, 80]. For example, Judy et al. [95] studied the importance of administering CoQ_{10} on the development of doxorubicin-induced cardiotoxicity in patients with lung cancer. A total cumulative dose of 600 mg/m^2 doxorubicin was given to patients, and those 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. In contrast, patients receiving the same dose of doxorubicin along with CoQ_{10}, cardiac function remained unchanged. The patients taking CoQ_{10} continued to receive doxorubicin until they received a total of 900 mg/m^2 doxorubicin, a dose at which approximately 50% of patients treated with doxorubicin alone would be expected to develop cardiomyopathy and congestive heart failure, but in those patients taking CoQ_{10}, the only change in cardiac function was a modest increase in heart rate. Other studies have confirmed these results and have shown that CoQ_{10} can reduce the cardiac toxicity of doxorubicin in adults [96, 97] and children [98, 99].

The above clinical studies [95-99] support the preclinical data indicating that CoQ_{10} protects the heart from the cardiotoxicity of anthracyclines. Similar to the preclinical studies,

however, the impact of CoQ_{10} on the antineoplastic efficacy of anthracycline-based chemotherapy was not studied.

6 Cancer-associated fatigue and co-morbid conditions

Fatigue is usually the most common complaint of patients undergoing anti-neoplastic therapy, but there are also other complaints including: pain, nausea, vomiting, malaise, diarrhea, headaches, rashes and infections [97, 99]. Other more serious problems can also occur, such as cardiomyopathy, peripheral neuropathy, hepatotoxicity, pulmonary fibrosis, mucositis and other effects [14,17, 97, 99]. Due to misconceptions among patients and their physicians, most patients feel that cancer therapy-associated fatigue is an untreatable symptom [100]. Although fatigue is usually the most commonly reported adverse symptom during cancer therapy, up until recently there was little effort directed at reducing fatigue before, during or after cancer therapy [101].

Reducing cancer-associated fatigue and fatigue associated with cancer therapy are now considered important goals, and psychological, physical, pharmaceutical and nutraceutical methods have been undertaken to reduce fatigue and improve the quality of life of cancer patients [102, 103]. These treatments are based on suppressing fatigue but also on controlling co-morbid or related symptoms, such as pain, anemia, cachexia, sleep disorders, depression and other symptoms [103-105].

Although there is no standard protocol related to treating cancer-associated fatigue and related symptoms, a review of the types of supportive measures used to control fatigue and related symptoms indicated that graded exercise, nutritional support, treatment of psychological problems, such as depression with certain anti-depressants or psycostimulants, treatment of anemia with hematopoetic growth factors and control of insomnia with cognitive behavioral therapy or pharmacological and nonpharmacological therapies all have a role to various degrees in controlling cancer-associated fatigue [103-107]. Interestingly, when some of these approaches were systematically analyzed in multiple (27) studies (meta-analysis) by Milton et al. [108], only a psycostimulant (methylphenidate) and hematopoetic growth factors (erythropoietin and darbopeitin) were more effective than placebo treatments. Other treatments were no better than placebo in the treatment of cancer-related fatigue [107].

7 Cancer-associated fatigue, aging and oxidative damage to mitochondria

Although cancer-associated fatigue has been defined as a multidimensional sensation [104, 105, 108], most patients understand fatigue as a loss of energy and inability to perform even simple tasks without exertion [21, 108, 109]. At the organism level cancer-associated fatigue involves the dysregulation of several interrelated physiological, biochemical and psychological systems [104, 105], whereas at the tissue and cellular levels fatigue is related to reductions in the efficiency of cellular energy systems, mainly found in mitochondria [110-112]. Damage to mitochondrial components, mainly by oxidation, can impair mitochondrial function and this can also result in oxidative stress caused by over-production of ROS/RNS (reviews [22, 28, 29]). Mitochondrial membranes and DNA are major targets of oxidative stress, and with aging ROS/RNS mitochondrial damage accumulates [113, 114].

In certain medical conditions as well as in aging oxidative damage to mitochondrial membranes impairs mitochondrial function [113-115]. For example, in chronic fatigue syndrome (CFS) patients there is evidence of oxidative damage to DNA and lipids [115, 116] as well as oxidized blood markers [117] and muscle membrane lipids [118] that are indicative of excess oxidative stress [119]. 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, increasing the rate of membrane damage [120].

8 Membrane lipid damage and replacement of oxidized membrane components

Mitochondrial membranes as well as other cellular membranes are especially sensitive to oxidative damage by ROS/RNS, which occurs at high rates in cancer [51, 52, 54-57, 119]. Oxidation of membrane phospholipids alters their structure, affecting lipid fluidity, permeability and membrane function [119, 121, 122]. One of the most important events caused by ROS/RNS damage is loss of electron transport function, and this appears to be related to mitochondrial membrane lipid peroxidation. Membrane oxidation induces permeability changes in

mitochondria, and this loss of transmembrane potential is an essential requirement of mitochondrial oxidative phosphorylation [123, 124].

One method to reverse the accumulation of damaged lipids in mitochondria and other cellular membranes is Lipid Replacement Therapy [110, 112]. Lipid Replacement Therapy 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 [110-112, 125]. Lipid Replacement Therapy has been found to be effective in preventing ROS/RNS-associated changes and reversing mitochondrial damage and loss of function [110-112].

Lipid Replacement Therapy with unoxidized lipid and antioxidant supplements 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 [110-112]. 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 [110-112, 125, 126]. NTFactor's encapsulated lipids are protected from oxidation in the gut and can be absorbed and transported into tissues via lipid carriers without oxidation. Once inside cells the membrane lipids naturally replace oxidized, damaged membrane lipids by natural diffusion and carrier proteins pick up the damaged lipids for degradation, transport and excretion [127].

In animal studies NTFactor has been used to reduce age-related functional damage. Using rodents Seidman et al. [128] 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 and prevented aging-related mitochondrial DNA deletions found in the cochlear. Thus NTFactor was successful in preventing age-associated hearing loss and reducing mitochondrial damage and DNA deletions in animals [128].

In clinical studies Molecular/Lipid Replacement Therapy has been used to reduce fatigue and protect cellular and mitochondrial membranes from damage by ROS/RNS [110-112]. A vitamin supplement mixture containing NTFactor was by used by Ellithorpe et al. [126] in a study of patients with severe chronic fatigue and was found 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 [129]. In addition, in a subsequent

study we examined the effects of NTFactor on fatigue and mitochondrial function in patients [111]. Oral administration of NTFactor for 12 weeks resulted in a 35.5% reduction in fatigue and 26.8% increase in mitochondrial function; whereas after a 12-week wash-out period fatigue increased and mitochondrial function decreased back to control levels [111]. Thus in fatigued subjects dietary Lipid Replacement Therapy can significantly improve and even restore mitochondrial function and significantly decrease fatigue. Similar findings were observed in CFS and Fibromyalgia Syndrome patients [125]. Recently a new formulation of NTFactor plus vitamins, minerals and other supplements resulted in a 36.8% reduction in fatigue within one week [130] (Table 1).

9 Lipid Replacement Therapy during cancer chemotherapy

Lipid Replacement Therapy 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 [131]. In two studies on advanced metastatic colon, pancreatic or rectal cancer patients receiving 5-florouracil/methotrexate/leukovorin therapy on a 12-week schedule Lipid Replacement was used to reduce adverse chemotherapy 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 slight 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 with Lipid Replacement [131]. In the double-blinded, cross-over, placebo-controlled, randomized part of the study on advanced cancers the patients on chemotherapy plus Lipid Replacement Therapy showed improvements in signs/symptoms associated with the adverse effects of chemotherapy [131]. Adding Lipid Replacement 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 on chemotherapy reported improvements in nausea, impaired taste, tiredness, appetite, sick feeling and other quality of life indicators [131] (Table 2). This clinical trial clearly demonstrated the usefulness of Lipid Replacement Therapy given during chemotherapy to reduce the adverse effects of cancer therapy.

10 Summary—Lipid Replacement Therapy in cancer patients

Lipid Replacement Therapy before, during and after cancer therapy of metastatic disease can significantly reduce the adverse effects of chemotherapeutic drugs and limit the oxidative stress-related damage to normal cellular structures. Such supplements can be used to replace normal cellular membrane lipid constituents that are damaged as a therapeutic consequence of excess oxidative stress as well as those damaged due to aging and other chronic conditions. Lipid 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. Thus Lipid Replacement Therapy is a cost-effective and safe method to reduce cancer-associated fatigue and the chronic and acute effects of cancer therapy on sensitive cellular membranes and other structures.

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Table 1 Effects of NTFactor®, a dietary Lipid Replacement supplement, on Piper Fatigue Scale scores (modified from Nicolson & Ellithorpe [125]).

Subjects/patients	n	age	Average Time on NTFactor	Piper Fatigue Scale fatigue reduction (%)	Reference
Chronic fatigue	34	50.3	8 wks	40.5**	Ellithorpe et al. [126]
Aging, chronic fatigue	20	68.9	12 wks	35.5*	Agadjanyan et al. [111]
CFS (and/or FMS‡)	15	44.8	8 wks	43.1*	Nicolson & Ellithorpe [125]
Aging, chronic fatigue	67	57.3	1 wk†	36.8*	Nicolson et al. [130]

**P<0.0001, *P<0.001 compared to without NTFactor®

‡FMS, fibromyalgia Syndrome, 5/15; CFS+FMS, 3/15

†Advanced Physician's Formula or Revacel with NTFactor®

Table 2 Effects of Propax with NTFactor® on the adverse effects of chemotherapy in a cross-over trial†*

First arm	Second arm	Average % patients on test arm§		
		improvement	no change	worsening
placebo	Propax(+NTFactor®)	57	22	21
Propax(+NTFactor®)	placebo	70	6	24

† Table reproduced with permission from Nicolson [112].

* The same regimen of 5-flurouracil/methotrexate/leukovoran was used for colon, pancreatic or rectal cancers.

§ The percent of patients self reporting adverse effects was averaged with the percent of patients with adverse effects reported by a research nurse.