Associations of Molecular-Genetic Bioenergetics and Chemotherapy-Induced Fatigue Symptoms in Patients with Breast Cancer: A proposal development

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Abstract

Introduction: Cancer-related fatigue (CRF) occurs in 82%-96% of cancer patients receiving chemotherapy (CT). CT-induced CRF is a distressing, persistent sense of exhaustion related to the disease or its treatment, and negatively impacts health outcomes. CRF is one of the most prevalent side effects of CT in patients with breast cancer. Despite various attempts to investigate the etiology of CRF, the biochemical mechanisms remain elusive.

Objectives: The study aims to explore the molecular-genetic pathway of mitochondrial bioenergetics and its association with CT-induced CRF. We hypothesized that the chemotherapeutic agent containing anthracycline targets cell cycle progression, which triggers genetic and cellular instability, altering expression of mitochondrial genes and proteins, inducing reduced electron transport chain enzymatic activity and impaired oxidative phosphorylation, resulting in adenosine triphosphate (ATP) depletion and excessive reactive oxygen species (ROS) generation, leading to the development and intensification of CRF.

Methods: This is a prospective, hypothesis-testing, and longitudinal study design. A total of 60 patients with breast cancer undergoing CT will be enrolled. Validated instruments will be used to measure CRF, depression, sleep disturbance, and physical activity. Whole blood sample will be collected before, during, and at the completion of CT to determine profiles of mitochondrial bioenergetics. A linear mixed model repeated measures analysis will be used to examine associations between changes in study variables.

Anticipated Results: Increased scores of CRF will be associated with altered mitochondria-related genes and mitochondrial bioenergetics (e.g., ↓oxidative phosphorylation, ↓electron transport chain complexes activity, ↓ATP content, and ↑ROS production) in patients receiving CT-containing anthracyclines.

Conclusion: The results will enable us to discover biomarkers, support the design of nonpharmacological interventions, and initiate precision symptom management to improve CRF.

Keyword: Cancer-related fatigue; Gene expression; Mitochondrial bioenergetics; Breast cancer; Chemotherapy

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Introduction

Breast cancer is the most common malignancy and the second leading cause of cancer mortality among women in the United States [1]. Alongside surgery and radiotherapy, one of the primary treatment modalities for women with early-stage breast cancer is chemotherapy (CT), alone or combined with hormone therapy [2]. While CT has significantly increased survival rates with this disease, it carries adverse clinical complications, including neutropenia, alopecia, cardiomyopathy, muscle wasting, and fatigue [3-6]. Of all treatment-related symptoms in cancer, fatigue is the most burdensome with the greatest adverse effect on quality of life [7,8].

Defined by National Comprehensive Cancer Network (NCCN), cancer-related fatigue (CRF) is pervasive, a whole-body excessive tiredness unrelated to activity or exertion and not relieved by rest or sleep [9,10]. CRF is very common during the treatment and causes long-lasting distress after the completion of treatment, even in disease-free stages [6,11-13]. CRF negatively impacts health outcomes including depression, sleep disturbance, impaired cognitive function, decreased physical activity, and poor quality of life [14-17]. Patients with breast cancer undergoing CT reported the poorest quality of life, with severe CRF, compared to those who received surgery or radiation therapy [18]. Factors that have been correlated with CRF severity in breast cancer patients receiving CT include depression, anxiety, poor sleep quality menopausal symptoms, and psycho-physiological factors [19-21]. Although various attempts have been made to investigate the etiology of CRF [22-30], the biochemical and pathophysiological mechanisms involved remain elusive. CT-induced CRF with multi-dimensions has not been well-characterized in patients with breast cancer.

There is no optimal effective pharmacologic therapy for CRF. The NCCN Practice Guidelines in Oncology for CRF currently recommend six nonpharmacological interventions: physical activity, physically based therapies, psychosocial interventions, nutrition consultation, cognitive behavioral therapy for sleep, and bright white light [9]. Using psychostimulants after other causes of CRF are ruled out that is the only pharmacologic intervention recommend by NCCN guidelines. Methylphenidate has been recommended, but two small, randomized clinical trials produced conflicting results [31]. With limited available options, evidence-based novel and precision strategies are needed to improve both pharmacologic and nonpharmacologic therapies for CRF. However, without a deeper more comprehensive understanding of precisely where and how CT impairs the metabolic cycle more robust testing of nutraceuticals, cannot be done. This study will provide that level of evidence.

Review of Literature

Previous studies have shown that nuclear genes regulating mitochondrial apoptosis, biogenesis, and bioenergetics in peripheral blood mononuclear cells (PBMCs) were associated with worsened CRF in prostate cancer patients receiving radiotherapy [32,33]. PBMCs of fatigued patients with cancer showed reduced ATP coupling efficiency compared to those without fatigue [34]. Platelet bioenergetics correlated with muscle energetics and fatigability in older adult [35]. Deficiency of adenosine triphosphate (ATP) has been proposed as the basis of fatigue in patients with cancer and chronic fatigue syndrome [36,37]. The mitochondrial respiratory chain is essential to produce and maintain an effective cell content of ATP [38,39]. Mitochondria generate 90% of ATP via oxidative phosphorylation (OXPHOS) and convert 0.4% to 5% of superoxide (O_2-) radical during normal mitochondrial OXPHOS. Mitochondria are vulnerable to reactive oxygen species (ROS), which are generated endogenously (e.g., mitochondrial superoxide) and exogenously (e.g., ionizing radiation, inflammation) [39].

Chemotherapeutic agents target rapidly dividing mitotic cells, trigger apoptosis, and cause the generation of excess ROS, which has been associated with mitochondrial dysfunction through increased mitochondrial ROS [4,40,41]. Doxorubicin is an effective antineoplastic agent and potent anthracycline antibiotic, and is widely used as a component of multiple-drug CT for breast cancer [42]. The cardiotoxicity of doxorubicin is characterized by a dose-dependent decline in cardiac function through increased ROS production in mitochondrial cardiac muscle [43]. Studies showed that epirubicin and doxorubicin induce a decrease in muscle strength and an accelerated rate of fatigue by interrupting mitochondrial energy metabolism and redox balance [42], as well as an associated worse quality of life [6]. Raised levels of ROS have also been associated with symptom development in patients with chronic fatigue syndrome [44]. CT has been associated with mitochondria dysfunction via increased mitochondrial ROS [45], eliciting significant side effects, including muscle fatigue [46]. ROS is considered one of the major, direct causes of ionizing radiation-induced damage [47], resulting in a number of adverse effects, including fatigue [48].

Both CT drugs and radiation-induced damage alter mitochondrial metabolism, inhibit the mitochondrial respiratory chain, and form highly reactive peroxynitrite (ONO_2-) [49,50]. Once mitochondrial proteins are damaged, the affinity of substrates or enzymes is decreased, resulting in mitochondrial dysfunction [38]. However, the studies that produced these findings did not identify the mechanism of inhibiting the mitochondrial respiratory chain related to

mitochondrial dysfunction and CRF after CT.

Preliminary Findings

Our preliminary work revealed that, over time, 14 mitochondrial-related genes were differentially expressed in men with localized prostate cancer during radiation therapy [33]. One downregulated gene, BC1 (ubiquinol-cytochrome c reductase) synthesis-like (BCS1L), and three upregulated genes: BCL2-like1 (BCL2L1); solute carrier family 25, member 37 (SLC25A37); and fission 1 homolog (S. cerevisiae) (FIS1); were associated with increased CRF (β = 1.3-2.4, p = 0.001- 0.002) at the end of treatment compared to baseline [32]. Altered expression of these genes was accompanied by changes of protein concentrations [32,33]. Worsened CRF was associated with impaired OXPHOS via complex III deficiency during radiotherapy in patients with prostate cancer [51-53]. BCS1L plays an important role in the assembly of complex III in the mitochondrial electron transport chain (ETC), which is essential for maintaining effective ATP levels [39,54].

Mitochondrial OXPHOS enzymes, proteins, and lipids are vulnerable to free radicals [55]. A defect in complex III leads to a functional deficit in the respiratory chain and impairs ATP production [54]. BCL2L1 is located on the mitochondrial outer membrane, regulating the opening of the membrane's voltage-dependent anion channel, controlling the production of ROS, and inducing cellular apoptosis [56]. SLC25A37 is a solute carrier localized in the mitochondrial inner membrane that serves as the principal iron importer. SLC25A37 plays a critical role in iron-consuming processes, including heme synthesis and Fe-S cluster synthesis in mitochondria [57,58]. Overexpression of SLC25A37 leads to increased iron uptake into mitochondria and promotes heme synthesis [58]; this increased matrix-free iron potentially increases hydroxyl radical formation from hydrogen peroxide and results in mitochondrial dysfunction [59,60]. In summary, our preliminary studies established that CRF is associated with mitochondria-related genes and impaired bioenergetics (e.g., $\downarrow$OXPHOS) in fatigued men treated with radiation therapy [32,33,52].

Characterization of both phenotype and molecular/ genotype of CT-induced CRF is imperative but has not been explored. We propose to investigate the molecular-genetic pathway of mitochondrial bioenergetics and its association with CT-induced CRF symptoms experienced by patients with breast cancer receiving CT-containing anthracyclines, compared to those with non-anthracycline-based CT. Understanding the mechanism/pathway underpinning CRF will enable the design of targeted therapeutics and non-pharmacological interventions, as well as to advance the science of symptom management.

Specific Aims

Our specific aims are to (1) characterize the profile of mitochondria-related genes associated with CRF symptoms, and (2) identify the profile of mitochondrial bioenergetics associated with CRF symptoms in patients with breast cancer receiving anthracycline-based CT, compared to patients with non-anthracycline-based CT at baseline, midpoint, and endpoint of CT, as presented in Figure 1.

Figure 1: Hypothesized Mitochrondrial Bioenergetic Pathways of CT-induced CRF.
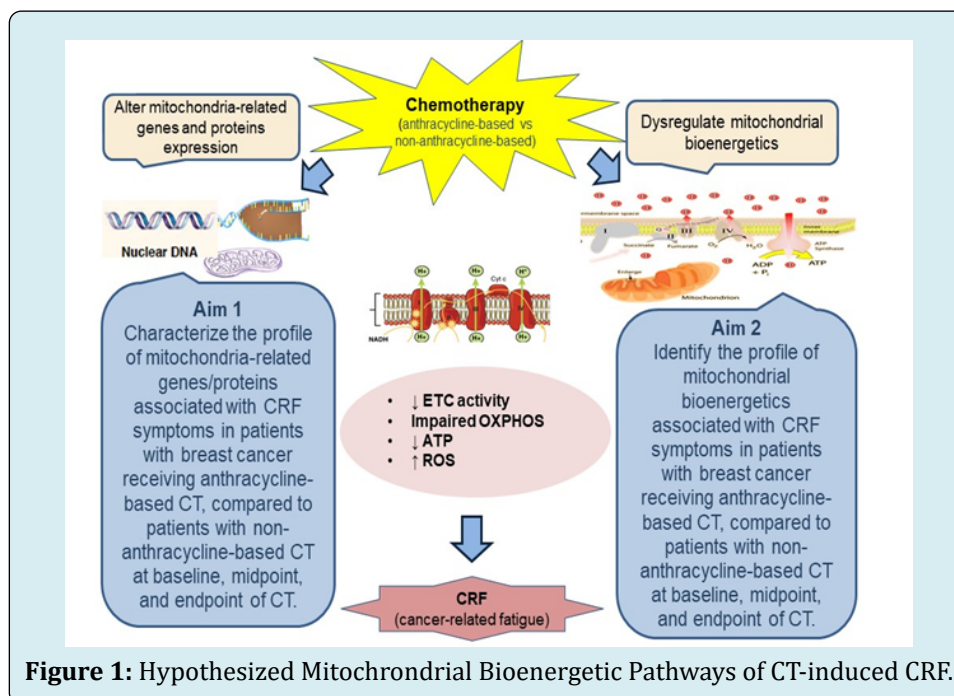
Hypothesis

We hypothesize that the chemotherapeutic agent containing anthracyclines will trigger changes in mitochondria-related genes and proteins, inducing a defect in ETC activity and impaired OXPHOS, leading to ATP depletion and excessive ROS generation, which are associated with developing and debilitating CRF.

Materials and Methods

This study is under reviewed by the Institutional Review Board (IRB) of University Hospitals and Case Comprehensive Cancer Center.

Design

This is a prospective, hypothesis-testing project using a longitudinal research design in patients with breast cancer receiving CT-containing anthracyclines (doxorubicin, epirubicin), compared to those with non-anthracycline-based regimens.

Sample and Setting

The study sample will be recruited from a population of breast cancer patients scheduled for CT. The study will be introduced to collaborating clinicians during one-on-one or team meetings at the study site, University Hospitals Seidman Cancer Center. The inclusion criteria are: (a) clinically confirmed early-stage (I-III) breast cancer; (b) anthracycline-based CT naive; (c) scheduled to receive a CT regimen with anthracycline-based (e.g., doxorubicin, cyclophosphamide, paclitaxel) or non-anthracycline regimen (e.g., docetaxel, cyclophosphamide); (d) able to provide written informed consent; and (e) ≥18 years of age. The exclusion criteria include: (a) progressive or unstable disease other than cancer of any body system causing clinically significant fatigue (e.g., class IV congestive heart failure, end-stage renal disease, stage IV chronic obstructive pulmonary disease), including systemic infections (e.g., HIV, active hepatitis, active COVID-19); documented recent (< 6 months) history of major depression, bipolar disease, psychosis, or alcohol/drug dependence/abuse; uncorrected hypothyroidism; untreated anemia; or chronic inflammatory disease (e.g., rheumatoid arthritis, systemic lupus erythematosus); (b) regularly taking antipsychotics or anticonvulsants, since these medications cause significant fatigue; (c) presence of second malignancies; (d) presence of mitochondrial disease; or (e) taking medication for fatigue (e.g., methylphenidate, moldafinil).

**Sample size:** We plan to enroll a total of 60 subjects (30 with anthracycline-based and 30 with non-anthracycline-based CT), which accounts for an attrition rate of 15-20% similar to previous studies [61,62].

Power analysis: Based on our preliminary work, the BCS1L expression values (mean + SD) at baseline, midpoint, and endpoint were 6.76+1.29, 7.88+1.63, and 7.89+1.36, respectively, in cancer patients with treatment, and changes from baseline to midpoint and endpoint were -1.12+0.93 and -1.13+0.85. With 50 patients (25 per group) treated with CT, there is >95% power to detect a significant increase in CRF during treatment and mean changes in BCS1L of -1.12 and -1.13 at the midpoint and endpoint, similar to results revealed in our pilot data, assuming similar standard deviations will be observed. The power is 80% to detect a mean change of -0.56, which is 50% of the effect seen in our pilot data. In addition, CRF severity increased significantly at midpoint (↑2.06+0.06, p< 0.05) and endpoint (↑2.71+0.14, p< 0.01) compared to baseline (1.45 +0.29) [51,53], similar to the findings from patients with breast cancer receiving CT [63,64]. Breast cancer patients receiving anthracycline-based CT experienced CRF severity increased threefold at the cycle 4 compared to baseline [65]. Assuming changes in CRF from baseline to endpoint in patients with anthracycline-based CT is twofold higher than those with non-anthracycline-based CT, the analytic sample size is expected to provide 80% power to detect a clinically meaningful difference of 3.4 in CRF changes from baseline to the endpoint between subjects with and without anthracycline-based CT. All calculations presented assume 2-sided tests with a significance level of 0.05.

Feasibility: The tumor registry of the study site shows that, in 2021, a total of 96 new patients with breast cancer were treated with CT at the University Hospitals Seidman Cancer Center. Assuming a 25% refusal rate and 10% ineligible rate as found in previous studies [61,62], this accrual rate (65%) would result in 60 patients with CT enrolled during the 12 month recruitment period.

Procedure

Data collection: CT for breast cancer patients usually is administered every 3 weeks for six cycles. To represent different phases of the CT and reflect the peak time of CRF, we chose three times to collect data: (1) baseline (prior CT, Day 0); (2) midpoint (during CT, Day 61-70, 3rd cycle of CT); and (3) endpoint (upon completion of CT, Day 126-140, 6th cycle of CT) [11]. Before starting the study, subjects will be screened for eligibility and then scheduled for data collection at their most convenient times. It will take less than an hour to complete all measures and blood work at each study visit. All tests and study visits will be conducted at the University Hospitals Seidman Cancer Center. Figure 2 presents the study procedure.

Figure 2: Study Procedure.
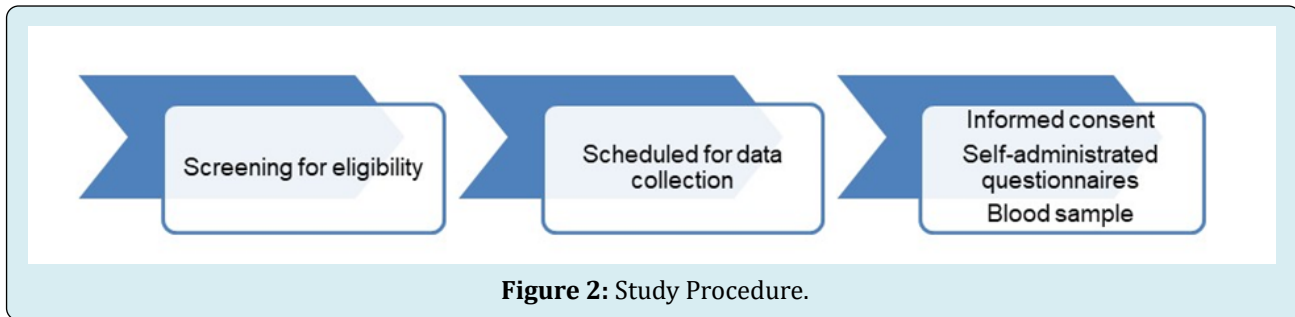
Blood draws and self-administered questionnaires will be coordinated with the patient's schedule for infusion. A total of 45 mL of blood will be collected at each time point from each subject. Blood samples will be kept at room temperature after collection and during transport to the mitochondrial research laboratory. PBMCs and platelets will be harvested from fresh blood anticoagulated with ethylenediaminetetraacetic acid (EDTA) within 24 hours after blood samples are collected, and either assayed immediately for bioenergetics or stored at -80ºC in a freezer for RNA extraction.

Study measures: biological and behavioral/psychosocial instruments. Demographics and clinical data (e.g., CT regimens, medications, CBC), as well as depression, sleep, and physical activity as covariates, will be collected.

Biological measures include (1) mitochondria-related gene/protein expression: (a) total ribonucleic acid (RNA) concentration, purity, and integrity will be tested after RNA extraction [26]. Extracted RNA will be converted to cDNA (complementary DNA) and stored at -20ºC until ready for gene expression. (b) Quantitative real time polymerase chain reaction (RT-PCR) will be used to detect expression values and changes in differentiated genes of mitochondrial bioenergetics. (c) Enzyme-linked immunoassay (ELISA) will be used to measure protein concentrations of differentiated genes, and data will be normalized and read in a microplate reader. (2) Mitochondrial bioenergetics: (a) the OXPHOS rate will be measured using validated protocols in the O2k high-resolution respirometry system [66,67]. The oxygraphy-2k (O2k, OROBOROS Instruments, Austria)) system provides robustness and reliability of instrumental performance, and has unique specifications; the limit of detection of respiratory flux is 1 pmol·s--1·cm-¬3 (0.001 µM·s-¬1) [68]. (b) ETC enzymatic activity will measured using spectrophotometry with validated protocols [67,69]. (c) The ATP content will be measured by bioluminescence assay; fluorometric method will be used to quantify the ROS production [70,71].

Behavioral and psychosocial assessments include (1) CRF: The revised Piper Fatigue Scale is a 22-item, paper/pencil questionnaire with excellent reliability and validity; specifically to measure multidimensions (i.e., severity, sensory, cognitive, and affective) of CRF in cancer patients [72]. CRF is defined as a score of > 6 [73,74]. (2) Depression: The Hamilton Depression Rating Scale is a clinician-rated paper questionnaire with 21-item, assessing the severity of depressive symptoms. Scores can range from 0 to 78; higher scores (> 17) [75] indicate greater severity of depressive symptoms. (3) Sleep: The Pittsburgh Sleep Quality Index is a 19-item index with high validity and reliability that measures subjective sleep quality [76]. (4) Physical activity: The International Physical Activity Questionnaire is a well-validated, 7-item, self-report questionnaire that gauges physical activity levels for the past 7 days [77].

Statistical Approaches and Analysis

The study objective is to examine the associations among mitochondrial genes, bioenergetics, and CRF symptoms over time in breast cancer patients receiving CT, and to compare differences in the profiles of gene expression, bioenergetics and CRF between patients with anthracycline-based CT and with non-anthracycline-based CT at baseline, midpoint, and endpoint of CT. When calculating summary scores for outcomes (e.g., Piper Fatigue Scale) based on summing scores of multiple items, unless specified otherwise in the documentation supplied for each measure, missing data in individual items will be handled by the following algorithm. If more than 50% of the items are missing, then the entire summary measure will be set to missing. If fewer than 50% of the items are missing, then the score will be computed after imputing the mean of the non-missing items for each non-missing item. To account for missing outcome variables, sensitivity will be analyzed using multiple imputations of follow-up outcomes with an inclusive strategy of analyzing more baseline variables in the imputation model [78]. We will use the Benjamin-Hochberg method for controlling the false discovery rate for each outcome, allowing for multiple testing.

Descriptive statistics (means, standard deviation, median, and range) will be used to summarize expression levels of differentiated genes and different dimensions of CRF at each time point. Data will be transformed using log

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or other transformations, if necessary, to better fit normality assumptions. Pearson or Spearman correlations will be used to examine the associations of CRF dimensions with expression of differentiated genes (Aim 1) and mitochondrial bioenergetics (Aim 2) at each time point. To compare the difference in gene expression, bioenergetics, and CRF severity between the CT group (anthracycline-based vs. non-anthracycline-based), we will use two-sample independent t-tests/Wilcoxon rank sum tests at each time point. Both aims will be analyzed using a linear mixed model repeated measures analysis to examine associations between changes in CRF dimensions and changes in expression of differentiated genes (Aim 1) and changes in mitochondrial bioenergetics (Aim 2) over time.

The linear mixed model will be included the CT group to assess group differences and the interaction term (CT group by change in expression of the differentiated gene for Aim 1 and CT group by change in bioenergetics for Aim 2) whether changes in CRF outcomes varied differently in changes in gene expression/bioenergetics between subjects with and without anthracycline-based CT. Further, to identify the important covariates, we will test one covariate (e.g., CT cycles, hormone therapy, depression, sleep, physical activity, age, and race) at a time to identify if the covariate has an impact on the analyses. In the linear mixed model, we will include identified covariates in the models to control for their effects. Statistical analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and SPSS version.

Anticipated Results

Compared to the baseline and those with non-anthracyclines, we expect to find increased/worsened CRF with different dimensions, altered mitochondrial gene expression ($p < 0.05$, > twofold change), and decreased bioenergetics (e.g., ↓oxidative phosphorylation, ↓electron transport chain complexes activity, ↓ATP content, and ↑ROS production) at midpoint and endpoint in patients receiving CT-containing anthracyclines. Furthermore, increased scores from different dimensions of CRF will be associated with altered mitochondrial genes; reduced OXPHOS, ETC activity, ATP content; and increased ROS.

Conclusion

We proposed a novel mechanism of mitochondrial bioenergetics for CT-induced CRF using molecular-genetic approaches. This will be the first study to determine the role of mitochondrial bioenergetics and its association with the development of debilitating CT-induced CRF. Currently, there are no effective and optimal evidence-based interventions for CRF. This research project is an essential step in pursuing a novel hypothesis designed to reveal the physiologic mechanisms of CRF, a ubiquitous cause of patient distress. There is some promising evidence that nutritional supplements can target relevant energy-producing processing, including ascorbic acid, niacin, vitamin E, and coenzyme Q10 [79].

Establishing the association of mitochondrial bioenergetics with CRF will provide a key foundation for devising clinical trials, such as cytoprotective interventions ranging from delivery of antioxidants to enhance individual antioxidant compacity to reduce ROS-related cellular damage and improve CRF.

Acknowledgements

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