TITLE: Clinical and Biological Predictors of Chemotherapy Toxicity in Older Adults

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1.0 PROTOCOL SUMMARY AND STUDY SCHEMA

Sixty percent of all cancers and 70% of cancer mortality occur in people greater than 65 years of age, defining cancer as a disease of older adults. Almost half of all new breast cancers in the United States are diagnosed in women 65 years of age or older\(^1\). Despite the association between cancer and aging, treatment recommendations and data acquired from prospective clinical trials in older women with breast cancer are sparse. As a result, physicians and older adults have limited data to guide treatment recommendation, make dose adjustments and manage toxicities in older adults. Aging is invariably associated with changes in physiology which can impact the pharmacokinetics and pharmacodynamics of cancer therapy. The potential for increased toxic effects in the older patient becomes an important concern. Therefore, it may not be reasonable to extrapolate data regarding toxicity from clinical trials, which primarily include younger, healthier patients. In addition, the age-related impact of adjuvant therapy on the functional status and quality of life of older versus younger adults has not been rigorously evaluated, and risk factors for toxicity, other than chronological age, need to be studied among older adults receiving chemotherapy.

The goal of this study is to develop a “bedside to bench” model of clinical and biological predictors for toxicity to adjuvant and neoadjuvant chemotherapy in older adults with breast cancer. We will develop a predictive model using clinical and biological predictors of toxicity to adjuvant and neoadjuvant chemotherapy in older adults with breast cancer. We will also determine the association between clinical and biological factors and reduced relative dose intensity of the prescribed chemotherapy regimen. In addition, we will explore specific chemotherapy toxicities associated with reduced relative dose intensity of a prescribed regimen.

Study Schema:

1) Identify all patients \(\geq 65\) years old with Stage I to III breast cancer who are beginning adjuvant or neoadjuvant chemotherapy

2) Describe the study to the patient: patient consents or refuses.

3) Prior to the start of chemotherapy, consenting patients are:
   a) administered a patient assessment (evaluation of functional status, comorbid medical conditions, cognitive function, psychological state, social support, social functioning, nutritional status) on the first day of treatment (prior to beginning chemotherapy) or up to 2 weeks before.
   b) will also have blood drawn for: routine laboratory values captured in daily practice; markers of inflammation and coagulation; and p16 expression, a potential marker of aging.

4) During therapy, information on the primary outcomes endpoints will be collected:
   a) Grade 2, 3, 4, or 5 toxicity;
   b) Hospitalization or urgent care visits during chemotherapy or up to 1 month following completion;
   c) Dose delay or reduction;
   d) Discontinuation of chemotherapy course;
   e) Chemotherapy type and dosing (planned and received)
   f) Supportive care medications

5) At the end of the chemotherapy regimen or up to one month later, consenting patients are:
   a) administered a patient assessment (evaluation of functional status, co-morbid medical conditions, cognitive function, psychological state, social support, social functioning, nutritional status)
   b) will also have blood drawn for: routine laboratory values captured in daily practice; markers of inflammation and coagulation; and p16, a potential marker of aging.
2.0 OBJECTIVES

Primary Objectives:

1. Develop a predictive model of clinical and biological predictors for grade 2-5 toxicity to adjuvant and neoadjuvant chemotherapy.

2. Understand the association between clinical and biological factors and reduced relative dose intensity (RDI) of the prescribed chemotherapy regimen.

3. Identify the specific chemotherapy toxicities associated with reduced relative dose intensity of the prescribed chemotherapy regimen.

Secondary Objectives:

1. Assess potential biomarkers for physiologic age, including interleukin-6, C-reactive protein, D-dimer, and p16 expression.

3.0 BACKGROUND

Breast cancer is the most commonly diagnosed cancer in American women and the second leading cause of cancer deaths. The greatest risk factor for breast cancer is age, and as the population ages, there will be a dramatic increase in the burden of breast cancer among older women. Adjuvant chemotherapy decreases the risks of relapse and mortality from breast cancer; however, older adults are at increased risk for chemotherapy toxicity, including an increased risk of treatment-related mortality. Balancing the benefits against the risks of adjuvant chemotherapy in the older patient population is challenging because of the dearth of evidence-based data to guide these decisions. While tools are available to provide an estimation of the benefits from adjuvant treatments, these tools do not provide an estimation of the risks of therapy. Furthermore, there is no consensus within the geriatric or oncology communities regarding a standard assessment of older patients with cancer that can stratify their risk for chemotherapy toxicity. While the geriatric literature has reported data on potential clinical and biological markers of aging and vulnerability, these are not typically utilized in daily oncology practice to assist in decision-making. This translational research will use a “bedside to bench approach” in order to develop a predictive model for adjuvant chemotherapy toxicity that consists of clinical and biological predictors. Furthermore, we will identify the relative dose intensity of chemotherapy received and the specific toxicities associated with inability to complete the prescribed chemotherapy course. This information would assist both the doctor and the patient in weighing the benefits and risks of chemotherapy treatment, and serve as a platform for future studies testing the efficacy of targeted interventions to decrease chemotherapy toxicity.

3.1. Adjuvant Chemotherapy for Older Adults with Breast Cancer: Why is a Predictive Model of the Potential Risks Needed? Adjuvant treatment decisions for older adults with cancer are complex for several reasons. First, there are less evidence-based data on which to base treatment recommendations for older adults or those in poor health. Most clinical trials, that set the standard for oncology care and provide data about the risks and benefits of adjuvant chemotherapy, enroll a low proportion of older adults. Therefore, the data regarding the risks and benefits are often extrapolated from studies of younger, healthier patients. For example, a review of 4 Cancer and Leukemia Group B trials for node positive breast cancer enrolled 6487 women; however, only 2% (n=159) were age ≥70. Second, patients with poor health or significant comorbidity are often excluded from these trials while the majority of older adults have comorbid medical conditions at the time of cancer presentation. Such comorbid medical conditions can introduce competing risk factors for mortality other than cancer and affect the ability to tolerate cancer therapy. Third, older adults are at increased risk of treatment-related toxicity, which could lead to reduced dose intensity and compromised efficacy of treatment. Lastly, adjuvant chemotherapy is given after the primary tumor is removed in order to decrease the risk of distant recurrence; however, there is no guarantee that the patient will benefit from this therapy. In sum, an accurate assessment of chemotherapy risks is needed in order to make an informed decision and carefully weigh the potential risks and benefits of adjuvant therapy.
3.2. Oncologist’s Clinical Evaluation of the Older Patient: Presently, oncologists assess functional status by assigning a Karnofsky performance status (KPS) or Eastern Cooperative Oncology Group (ECOG) performance status.47-48 These generic scales are applied to all adult cancer patients, regardless of age, and are used to estimate functional status in order to determine a treatment course, assess eligibility for clinical trials, and predict treatment toxicity and survival. KPS and ECOG performance status have been shown to independently predict survival, regardless of age.49-53 However, these tools may result in misleading decisions for the older patient, since clinical trials relying on these scales have largely excluded elderly patients. A prospective study of 500 older adults with cancer demonstrated that KPS could not identify older adults at risk for chemotherapy toxicity but a predictive model, including geriatric assessment questions, could identify those individuals.54 The oncologist also reviews the older adult’s comorbid medical conditions and laboratory data; however, there is no routine algorithm utilized in daily practice to integrate and weigh these parameters in assessing treatment tolerance or survival.

3.3. Geriatrician’s Clinical Evaluation of the Older Patient: The geriatrician’s evaluation (called a “geriatric assessment”) includes an assessment of a patient’s functional status, comorbid medical conditions, cognition, psychological status, social functioning and support, and nutritional status. Each of these domains is an independent predictor of morbidity and/or mortality in the geriatric population.11-16, 55 This comprehensive evaluation identifies areas of vulnerability among all geriatric patients, not just those with cancer, and provides valuable information not provided by KPS or ECOG performance scores.54 however, this assessment is not commonly taught in oncology training or utilized in oncology practice. A description of each geriatric assessment domain and its relevance to the older patient with cancer is provided below.

3.3.1. Functional Status: Cancer is associated with an increased need for functional assistance (measured by ability to complete activities of daily living) independent of KPS or ECOG performance status.56 Among patients with cancer, the need for functional assistance predicts chemotherapy toxicity, postoperative complications, and survival.56-59 Oncologists need an accurate tool to assess functional status in order to determine the risk of treatment toxicity, determine whether the patient can seek medical attention if necessary (ie, use the telephone, follow instructions, and anticipate and respond to toxicity), and estimate overall survival.

3.3.2. Comorbid Medical Conditions: Among patients with cancer, an increased burden of comorbidity is associated with poorer overall survival.60-64 Several studies have demonstrated the impact of comorbidity on cancer treatment tolerance.61, 65-67 Furthermore, these comorbid conditions may require treatment with multiple medications, predisposing the patient to the risks of polypharmacy and drug interactions.

3.3.3. Cognition: A cognitive assessment is needed to determine if the patient has the decisional capacity to consent and adhere to supportive-care medication instructions and understand the indications to seek attention if toxicity occurs. In the presence of cognitive impairment, the involvement of the patient’s family or caregiver is often required to maintain safety. Studies in patients without cancer have demonstrated an association between cognitive function and physical function.68-70

3.3.4. Psychological State and Social Support: In a study of older adults with cancer, significant distress was identified in 41% of older adults and poorer physical function correlated with higher distress.71 Among older adults without cancer, depressive symptoms are associated with a decline in physical function.72 In both the geriatric and oncology literature, social isolation has been linked to an increased risk of mortality.11, 55, 73-74 Social support serves as a buffer against the psychological impact of a stressful life event. 75-76

3.3.5. Nutrition: Poor nutritional status is associated with an increased need for functional assistance and poorer overall survival in the geriatric population.77 Among patients with cancer, unintentional weight loss during the 6 months prior to chemotherapy was associated with poorer survival, lower chemotherapy response rates, and decreased performance status.78

3.4. Biological Predictors of Aging and Vulnerability:

3.4.1. Criteria Applied to Choosing Biological Predictors: There are many potential biological predictors of aging that were considered when formulating this research proposal. A review was conducted of a comprehensive list of potential biological predictors identified through 4 primary sources: 1) the 2004 American Geriatrics Society, National Institute on Aging conference in a “Research Agenda for Frailty in Older Adults;”75 2) the 2007 American Association for Cancer Research (AACR) Conference on
“Translational Research at the Aging and Cancer Interface,” the 2008 American Federation For Aging (AFAR) Research Conference on “Aging and Cancer: Two Sides of the Same Coin?” and the 2010 U13 conference (PI: Huria) of the Cancer and Aging Research Group in collaboration with the NIA and NCI on “Biological, Clinical, and Psychosocial Correlates at the Interface of Aging & Cancer Research.” The following criteria were applied to select the biological predictors included in this protocol: 1) scientific potential to identify older adults with decreased physiologic reserve; 2) availability of preliminary data in the geriatric and oncology populations; and 3) ease of use in daily practice (i.e., a blood marker was preferable to a tissue-based marker). These 3 criteria were weighed equally. In addition, we wanted to include at least 1 molecular marker and 1 or more markers of physiology. After comprehensive review, the following potential biomarkers of aging, which can be measured from a peripheral blood sample, were chosen: 1) markers of inflammation and coagulation: Interleukin-6 (IL-6), C-reactive protein (CRP), D-Dimer; 2) a potential molecular marker of aging: p16^{INK4a} expression; and 3) measures of organ function included in routine blood work.

3.4.2. Inflammation, Coagulation, and Physiologic Dysregulation in Older Adults: It has been hypothesized that aging is associated with a dysregulation in inflammation and coagulation. There is an age-associated increase in levels of pro-inflammatory cytokines such as IL-6 and CRP. Increased levels of inflammation and coagulation have been associated with functional decline and mortality. Higher levels of D-Dimer and IL-6 at baseline were associated with subsequent functional decline and mortality in a cohort of 1,723 older adults. Serum measures of inflammation (CRP) and coagulation (Factor VIII, D-Dimer) were associated with clinical frailty among 4,735 community-dwelling adults age ≥ 65. Higher levels of IL-6 and CRP were associated with poor walking speed and grip strength, as well as cognitive decline in older adults. Among patients with operable breast cancer, elevated plasma D-Dimer levels were markers of lymphovascular invasion, higher clinical stage, and lymph node involvement. Some studies have suggested that CRP is associated with cancer risk, although other studies have not confirmed these findings.

3.4.3. Expression of p16^{INK4a} as a Biomarker of Aging: Mounting evidence is demonstrating that p16^{INK4a}, a tumor suppressor that originates from the INK4/ARF locus on chromosome 9p21, is a potential molecular marker of aging. Expression of p16^{INK4a} increases with age in mammalian tissues, including human, rodent, and baboon. In mice, p16^{INK4a} expression is associated with an age-related decline in hematopoietic stem cells, neural stem cells, and pancreatic islet cells. In a progeroid mouse strain, inactivation of p16^{INK4a} can partially rescue several age-related phenotypes. Single nucleotide polymorphisms near the INK4/ARF locus are associated with age-related conditions including frailty, atherosclerotic disease, and diabetes mellitus. Furthermore, in mice, chemotherapy and total body irradiation induce p16^{INK4a} expression.

In a study of 170 healthy donors, expression of p16^{INK4a} was found to increase with age (Fig 1), p16^{INK4a} expression was associated with plasma IL-6 concentrations and with age-related activities that increase frailty and vulnerability, such as smoking and physical inactivity. These data demonstrate that p16^{INK4a} is a potential molecular marker of aging and physiologic reserve. Sharpless and colleagues developed a means of characterizing p16^{INK4a} expression in peripheral blood.

3.4.4. Age and Hematologic, Renal, and Hepatic Function: With increasing age, there is a decrease in bone marrow reserve. In the geriatric population, anemia is associated with an increased risk of hospitalization, morbidity, and mortality. Among older adults with cancer, the age-related decrease in bone marrow reserve is associated with an increased risk of myelosuppression and associated complications from chemotherapy. Further, several studies have demonstrated the importance of renal and hepatic function when dosing chemotherapy. Over a lifespan, renal mass decreases by 25% to 30% and glomerular filtration rate decreases 0.75 ml/minute/year after age 40. Hepatic mass and blood flow decrease with age. The cytochrome P450 content in liver biopsy samples decreases by approximately 30% in patients age >70. Age-related changes in bone marrow reserve, renal, and hepatic function could impact the risk of chemotherapy toxicity.

3.5. Chemotherapy Toxicity and Decreased Relative Dose Intensity (RDI): Adjuvant chemotherapy decreases the risk of relapse and mortality from breast cancer; however, efficacy depends on the RDI
delivered. A landmark study by Bonnadona and colleagues evaluated the association between RDI (defined as the proportion of the standard reference dose intensity received) and chemotherapy efficacy. Patients who received <85% RDI had poorer relapse-free and overall survival.\(^{116-117}\) While prospective and population-based studies have demonstrated a benefit from adjuvant chemotherapy in older adults with breast cancer, data from the Early Breast Cancer Trialists’ Collaborative Group meta-analysis (including over 150,000 women with breast cancer from 194 randomized trials) demonstrates decreasing benefit from adjuvant chemotherapy with increasing age.\(^5\) A potential etiology for the age-related decrease in chemotherapy efficacy is a decrease in RDI secondary to toxicity. Lyman and colleagues evaluated the incidence and predictors of low dose intensity in 19,898 community-based patients with early stage breast cancer and demonstrated that patients age \(\geq 65\) were at risk for a reduced RDI with 66.5% receiving a RDI of <85%.\(^{118}\)

3.6. Conceptual Model: The conceptual model (Fig 2) encompasses clinical variables (sociodemographic, tumor, treatment, and geriatric assessment variables) and biological variables (renal function, hepatic function, hemato logically function, and potentially novel biomarkers of aging [markers of inflammation and coagulation, and a molecular marker of aging, \(p16^{INK4a}\)]). These clinical and biological variables will be used to develop a predictive model for chemotherapy toxicity. The association between chemotherapy toxicity and relative dose intensity will be evaluated.

![Figure 2. The Conceptual Model: Clinical and Biological Predictors of Chemotherapy Toxicity*](image)

* Arrows on periphery signify the potential interaction between all biological and clinical predictors of toxicity

3.7. Preliminary Studies:

3.7.1. Preliminary Data Regarding Adjuvant Chemotherapy in Older Adults with Breast Cancer:

3.7.1.a. Association between age and health status in adjuvant treatment decisions: Hurria et al surveyed oncologists (N=151) and primary care physicians (PCPs) with geriatric expertise (N=158) regarding treatment recommendations for older patients with breast cancer. Most oncologists and PCPs recommended some form of adjuvant therapy for older patients of all ages (70, 75, 80, and 85) and health status. Both oncologists and PCPs were less likely to recommend treatment as a patient’s age increased or health status declined \((P < .0001)\), demonstrating that age and health status influence treatment recommendations. These results highlight the need for evidence-based guidelines for breast cancer treatment in older adults taking into account age, health status and age-related toxicities of therapy. Collaboration between oncologists and geriatricians can help to accomplish this goal.

3.7.1.b. Efficacy and toxicity to adjuvant chemotherapy in older adults: A prospective randomized study (led by co-investigator Dr. Muss) of patients age \(\geq 65\) with stage I-III breast cancer demonstrated superior disease-free and overall survival with standard poly-chemotherapy (AC or CMF) in comparison to single-
agent capecitabine. Muss et al performed a review of CALGB studies for node-positive breast cancer, and demonstrated that older adults derive similar benefit from adjuvant treatment as younger adults; however, older adults are at increased risk for toxicity. Hurria et al reviewed a consecutive cohort of 132 patients, age ≥65 (mean age 70), who received adjuvant breast cancer chemotherapy. Patients who received an anthracycline based regimen (compared with a non-anthracycline-based regimen) were more likely to experience grade 3 or 4 toxicity ($P=.01$), require hospitalization ($P<.001$), and/or develop febrile neutropenia ($P<.001$). In another cohort of 162 patients (mean age 66) who received dose dense chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel), 50% experienced a treatment delay or grade 3 or 4 toxicity; however the risk of toxicity depended more on comorbidity and baseline hemoglobin value than patient age. Hurria et al demonstrated that an increased creatinine or decreased creatinine clearance was associated with an increased risk of febrile neutropenia and hematological toxicity among older adults receiving adjuvant breast cancer chemotherapy. Hurria et al also studied the impact of adjuvant chemotherapy on the older adult’s functional status, quality of life and cognitive function.

3.7.2. Developing a Geriatric Assessment Tool to Evaluate the Health Status of Older Adults with Cancer: Health status influences oncology treatment decisions and outcomes; however, there is no standard tool available with which to assess the health status of an older adult with cancer. In order to address this void, Dr. Hurria and co-investigators in the current proposal have developed and field-tested a Geriatric Assessment Tool designed specifically for older patients with cancer. The assessment includes an evaluation of domains predictive of morbidity and mortality in older adults including functional status, comorbid medical conditions, cognition, psychological state, social functioning, social support, and nutrition. To construct the Geriatric Assessment Tool, the geriatric and oncology literature was reviewed to choose commonly used, validated geriatric assessment measures. Selection criteria included: reliability, validity, brevity, the ability to self-administer, and the ability to prognosticate risk for morbidity or mortality in an older patient. The final selection of measures was reviewed and approved by the Cancer and Leukemia Group B (CALGB) Cancer in the Elderly and Quality of Life Committees. The initial feasibility study of this tool was conducted at Memorial Sloan-Kettering Cancer Center and the University of Chicago. Forty patients (mean age 74, range 65 to 87) with various types of cancer participated in the study. The geriatric assessment was feasible, as demonstrated by a mean time to completion of 27 minutes, 90% of patients were satisfied with the questionnaire length, and 78% were able to complete the self-administered portion on their own.

3.7.3. Incorporating the Geriatric Assessment Tool in Oncology Clinical Trials (CALGB 360401): CALGB 360401 evaluated the feasibility of incorporating the Geriatric Assessment Tool into oncology cooperative group trials. Patients were eligible to participate if they were age ≥65 and had signed consent for a cooperative group treatment trial. The Geriatric Assessment Tool was completed prior to initiation of the protocol-specified treatment. Ninety-three patients enrolled in this study. The median time to complete the assessment was 22 minutes, 88% of patients completed the patient portion without assistance, 88% were satisfied with the assessment length, 98% reported there were no upsetting items, and 95% said the assessment was easy to comprehend. The Geriatric Assessment Tool met the protocol specified feasibility criteria for incorporation in oncology cooperative group trials.

3.7.4. Can the Geriatric Assessment Predict Chemotherapy Toxicity? (Cancer & Aging Research Group Multicenter [CARG] Study 06170): The goal of this multicenter study was to utilize the Geriatric Assessment Tool to identify clinical predictors of chemotherapy toxicity in older adults with cancer who were receiving standard chemotherapy treatment. Patients age ≥65 with cancer received the Geriatric Assessment Tool prior to receipt of a new chemotherapy regimen. The primary objective of this study was to determine if the Geriatric Assessment Tool predicted grade 3-5 toxicity using the NCI Toxicity Index, Common Terminology Criteria for Adverse Events (CTCAE, V3.0). Among the 500 enrollees, the mean age was 73 years (range 65-91). The most common tumor types were lung (29%), GI (29%) and breast/gynecologic (22%) cancers; 61% had stage IV disease and 71% received 1st line chemotherapy. The assessment revealed a number of findings that would not have been detected on routine history and physical exam: 41% of patients needed assistance with instrumental activities of daily living despite a mean physician-reported KPS of 85 (range 50-100); 92% had ≥1 comorbid medical conditions (mean 2.5; range 0-9); 95% took ≥1 medications (mean 5; range 0-23); 16% had ≥1 falls in the past 6 months; 6% had gross cognitive impairment on the cognitive screening test, and 39% had >5% weight loss in the past 6 months.
Grade 3-5 toxicity occurred in 53% (50% grade 3, 12% grade 4, 2% grade 5). Risk factors for grade 3-5 toxicity included: 1) age ≥ 73, 2) cancer type (GI or GU), 3) standard dose, 4) poly-chemotherapy, 5) falls in last 6 months, 6) assistance with instrumental activities of daily living, and 7) decreased social activity. A risk stratification schema (number of risk factors: % incidence of grade 3-5 toxicity) was developed - 1: 23%; 2: 36%; 3: 50%; 4: 60%; 5: 83%; 6: 90%; 7: 100%. Of these 500 patients, 183 patients received adjuvant chemotherapy and 38 patients had stage I-III breast cancer. Of those 38 patients, 53% had grade 3-4 toxicity, 29% had a dose reduction, and 21% experienced a dose delay.

3.8. Goals of Current Study

Although cancer is a disease associated with aging, there is no standard tool in oncology practice that incorporates clinical and biological factors to identify older adults with cancer who may be more vulnerable to the toxicity of chemotherapy. It is generally recognized that chronological age tells relatively little about an older adult’s physiological age. Oncologists allude to this when they describe an older adult as: “a ‘young’ 80-year-old” or “an ‘old’ 80-year-old,” implying factors other than age contribute to the health status of an older adult. Geriatricians address this by routinely performing a “geriatric assessment,” which measures independent clinical predictors of morbidity and mortality in older adults. In addition, several potential biomarkers of aging have been described that are associated with functional decline and mortality among older adults. This study will identify whether novel biomarkers of aging can predict risk of chemotherapy toxicity. The current proposal will fill this knowledge gap by melding the principles of geriatrics with those of oncology to create a tool to assess the clinical and biological risk factors for chemotherapy toxicity in older adults.

Furthermore, this study will determine the association between chemotherapy toxicity and dose reductions and/or delays that decrease chemotherapy dose intensity. Maintenance of chemotherapy dose intensity is necessary to maintain chemotherapy efficacy. Older adults are at risk for chemotherapy toxicity and if this toxicity results in decreased dose intensity, the benefits of chemotherapy will be compromised. This study will identify the association between clinical and biological predictors of grade 2-5 toxicity and relative dose intensity. Furthermore, this study will identify the specific dose-limiting toxicities. These data will provide evidence-based criteria to identify those patients whose projected risk of toxicity would limit dose intensity and compromise the efficacy of standard treatment. These data could serve as the basis for “vulnerable elderly trials” which would study an alternate therapy regimen in patients who are predicted to have a significant risk of toxicity (and compromised efficacy) with the standard regimen.

This proposal unites the fields of geriatrics and oncology, incorporating geriatric correlates of vulnerability and studying their impact in an aging oncology population. These data will be used to develop a predictive equation for the risk of chemotherapy toxicity that can be utilized in daily oncology practice. These data will facilitate decision-making regarding the risks and benefits of adjuvant chemotherapy in older adults with breast cancer and ultimately serve as a foundation on which to identify older adults at risk for chemotherapy toxicity in order to guide interventions to decrease this risk.

4.0 METHODS

1) Identify all patients ≥ 65 years old with Stage I to III breast cancer who are beginning adjuvant or neo-adjuvant chemotherapy

2) Describe the study to the patient: patient consents or refuses.

3) Prior to the start of chemotherapy, consenting patients are:
   a) administered a patient assessment (evaluation of functional status, co-morbid medical conditions, cognitive function, psychological state, social support, social function, nutritional status) on the first day of treatment (prior to beginning chemotherapy), or up to 2 weeks before.
   b) will also have blood drawn for: routine laboratory values captured in daily practice; markers of inflammation and coagulation; and p16 expression, a potential marker of aging.

4) During therapy, information on the primary outcomes endpoints will be collected:
   a) Grade 2, 3, 4, or 5 toxicity;
   b) Hospitalization or urgent care visits during chemotherapy or up to 1 month following completion;
5.0 CRITERIA FOR SUBJECT ELIGIBILITY

Inclusion Criteria
1. Patients with stages I-III breast cancer receiving adjuvant or neoadjuvant chemotherapy
2. Able to understand English
3. Able to provide informed consent
4. Patients age ≥65 and of any performance status are eligible

Exclusion Criteria
1. Patients with metastatic disease

6.0 STUDY DESIGN

6.1 Research Design and Methods

5) At the end of the chemotherapy regimen or up to one month later, consenting patients are:
   a) administered a patient assessment (evaluation of functional status, co-morbid medical conditions, cognitive function, psychological state, social support, social functioning, nutritional status).
   b) will also have blood drawn for: routine laboratory values captured in daily practice; markers of inflammation and coagulation; and p16, a potential marker of aging.

6) Demographic information will be collected on any subjects that decline enrollment in this trial in order to determine whether there are different demographic characteristics among patients who decline the protocol or agree to participate.

6.2. Overview of Study Design: This is a prospective longitudinal study of 500 adults age ≥65 with stage I-III breast cancer who are going to receive adjuvant or neoadjuvant chemotherapy. Eligible patients will undergo an informed consent process. Those who agree to participate in this study will undergo a pre-chemotherapy clinical and biological assessment. Patients will subsequently receive standard of care adjuvant chemotherapy as prescribed by the treating physician. Chemotherapy drugs and doses (planned and actual received throughout the entire course) will be recorded, as well as supportive care medications, including white blood cell growth factors. Patients will be followed throughout the course of chemotherapy (from start to 1 month post-completion of chemotherapy) to capture NCI CTCAE (v4.0) grade 2-5 toxicities. Hospitalizations, dose delays, reductions, and discontinuation of chemotherapy will be captured, as well as the relationship of these events to toxicity.
6.3. **Study Sample:** This is a prospective longitudinal study of adults age ≥ 65 with stage I-III breast cancer who are to receive adjuvant or neoadjuvant chemotherapy. Patients must read and understand English since not all geriatric assessment measures have been validated in other languages. Eligible patients who are interested in participating in the study will undergo the informed consent procedure. With IRB and patient permission, demographic information will be collected on patients who decline enrollment in this trial in order to determine if there are different demographic characteristics among those who decline and those who participate. Patients who decline participation in the study will be asked for permission to capture the following demographic information.

1) age (if the patient is ≥ 90, then age will not be captured)
2) race
3) ethnicity
4) reason for declining enrollment

The rationale for capturing this information will be described to the patient (ie, to determine if there are differences in the demographic information between patients who enroll on the study and those who do not enroll on the study). The patient may agree or decline to provide this information.

6.3.1 **Recruitment:** Patients will be recruited from the outpatient clinic practices at the following participating institutions: City of Hope, Memorial Sloan-Kettering Cancer Center (MSKCC), Yale University School of Medicine, University of Rochester, University of North Carolina, Wake Forest University, and Case Western Reserve University.

6.4. **Clinical Assessment (Appendix I and II):** The clinical assessment is completed “pre-chemotherapy” (defined as prior to the start of treatment on the day 1 of the 1st cycle of adjuvant or neoadjuvant chemotherapy or up to 2 weeks before) and at the end of chemotherapy or up to one month later. Appendix I is completed by the research assistant. Appendix II is completed by the patient (with data reviewed by a research assistant for completeness). Patients who cannot complete Appendix II on their own will receive assistance from a research assistant. The reason for requiring assistance will be noted.

The clinical assessment is described below:

6.4.1. **Sociodemographics (Appendix I):** patient age, race, ethnicity, highest level of education achieved, marital status, and presence of a living companion

6.4.2. **Tumor and Treatment Characteristics (Appendix II):** tumor stage, surgery type, breast irradiation (pre-chemotherapy), the planned and received chemotherapy type, dosing and schedule, and supportive care medications

6.4.3. **Geriatric Assessment Variables (Appendix I and II):**

6.4.3.a. **Functional Status:**

   a) **Instrumental Activities of Daily Living (IADL):**\(^\text{125}\) (Subscale of the Multidimensional Functional Assessment Questionnaire [MFAQ]: Older American Resources and Services [OARS]): The OARS MFAQ was developed to provide a profile of the level of functioning and need for services of older persons who live at home but may have some degree of impairment. It has been tested in over 6,000 older community residents. The IADL subscale consists of 7 questions rated on a 3-point Likert scale measuring degree to which an activity can be performed independently. Five week test-retest correlation is 0.71 for the IADL subscale.\(^\text{125}\)

   b) **Medical Outcomes Study (MOS) Physical Health Scale:**\(^\text{126}\) The MOS Physical Health Scale measures a broad range of physical functioning, with questions ranging from “Can you bathe and dress yourself?” to “Can you perform vigorous activities, such as running or lifting heavy objects?” Items are rated on a 3-point Likert scale measuring independence in performing the activity. Internal consistency of the scale is 0.92.\(^\text{126}\)

   c) **Karnofsky Performance Status (KPS) Scale (Healthcare Professional Rating):**\(^\text{47}\) The KPS scale is a general measure of patient independence in carrying out normal activities and self-care needs. Patients are given a score on a numerical scale of 0-100 as a global indicator of functional status. KPS correlates with variables related to physical functioning (difficulty with stairs, difficulty with balance); Pearson correlation 0.63 \([P<.001]\) and 0.61 \([P<.001]\) respectively).\(^\text{47, 127}\)
d) Karnofsky Self-Reported Performance Status Scale. A self-report version of the KPS scale was developed to assess the patient’s perception of his/her own performance status, choosing from a range of functioning from “able to carry out normal activities requiring no assistance” to “severely disabled, requiring continuous nursing care.” Among patients with cancer participating in clinical trials, the patient rated KPS was significantly related to survival \((P < .05)\), and provided information independent from that obtained by the physician-rated KPS. 

e) Timed Up and Go: The Timed Up & Go is a performance based test of functional status, measuring how many seconds it takes to stand up from a standard arm-chair, walk 3 meters (10 feet), turn, walk back to the chair, and sit down again. In community-dwelling older adults, there was good inter- and intra-rater reliability (intraclass correlation coefficient 0.99 for both). The Timed Up & Go score correlated to the scores on the Berg Balance Scale \((r = -0.72)\), gait speed \((r = -0.55)\), and Barthel Index of Activities of Daily Living \((r = -0.51)\).

f) Number of Falls in Last 6 Months: Older patients are at higher risk for falls because of limited mobility, gait, and balance impairments. Patients will be asked to report their number of falls in the last 6 months.

6.4.3.b. Comorbidity: Physical Health Section (Older American Resources & Services Questionnaire [OARS]). The OARS Physical Health Section is a comorbidity scale consisting of a list of comorbid conditions and the degree to which they impair daily activities, rated on a 3-point scale of “not at all” to “a great deal.” Test-retest reliability over 5 weeks was 0.66. In terms of validity, the Physical Health Section correlated significantly with health professional ratings (Kendall’s tau coefficients: 0.75).

6.4.3.c. Cognition: Blessed Orientation-Memory-Concentration Test (BOMC). The BOMC consists of 6 questions designed to screen for gross cognitive impairment. The test-retest reliability is high (Spearman Rank Correlation 0.96; \(P < 0.001\)). The BOMC has excellent validity as a screening instrument, correlates highly with clinicians’ ratings of dementia severity \((r = 0.89)\), predicts results from a longer (26 item) mental status questionnaire, and discriminates between patients with mild, moderate, and severe cognitive deficits.

6.4.3.d. Nutritional Status:

a) Percentage of Unintentional Weight Loss in Last 6 Months: The effect of unintentional weight loss in patients with cancer was evaluated in a study of 3,047 patients enrolled in ECOG chemotherapy trials. Weight loss during the 6 months prior to chemotherapy was associated with poorer survival (statistically significant in 9 out of 12 tumor types) and lower chemotherapy response rates (significant in patients with breast cancer).

b) Body Mass Index (BMI): In a prospective study of 214 older community-dwelling adults, a BMI < 22 kg/m² was associated with the need for assistance with activities of daily living \((OR 1.21; 95\% CI: 1.01-1.45)\) and decreased 1-year survival \((RR 0.85 [95\% CI: 0.74-0.97])\).

6.4.3.e. Psychological Status: Mental Health Inventory (MHI)-17: The MHI is based upon the General Well-Being Scale developed by Dupuy for the National Health Interview Survey and has community norms, based upon 5,000 respondents from 6 communities. In order to reduce respondent burden, a 17-item version (shortened from the 38-item version) of the MHI will be used, which will yield 3 global scores of Psychological Distress, Psychological Well-Being, and the MHI total score. The MHI-17 has an excellent internal consistency \((alpha coefficient: 0.96)\).

6.4.3.f. Social Functioning: Medical Outcomes Study (MOS) Social Activity Limitations Measure: The impact of cancer on patients’ social functioning will be assessed by the MOS Social Activity Limitations scale. The 4-item scale includes the extent to which physical or emotional problems have interfered with social activities. All items are rated on a 5-point Likert scale. Internal consistency was good \((alpha coefficient = .77)\). The scale correlates with a range of measures: role limitations due to physical health \((r = .52)\), emotional health \((r = .49)\), psychological distress \((r = .64)\), and pain \((r = .55)\).

6.4.3.g. Social Support: Medical Outcomes Study (MOS) Social Support Survey: The scale was tested on 2,987 patients and designed to assess quality of life of patients across medical conditions. All but 1 item is rated on a 5-point Likert scale from ‘None of the Time’ to ‘All of the Time.’ Internal consistency of the subscales and total score are excellent \((alpha coefficient ≥ 0.91)\). Convergent validity is demonstrated by correlations of social support total score with measures of mental health \((r = 0.45)\).

6.4.3.h. Quality of Life: Functional Assessment of Cancer Therapy-General: FACT-B Functional Assessment of Cancer Therapy Scale is a previously validated scale which produces an overall quality of life measurement, as well as subscale scores for physical, functional, social, emotional well being,
and satisfaction with the treatment relationship. A disease specific FACT scale has been developed, pertaining particularly to breast cancer patients.

### 6.5. Biological Assessment:
The biological assessment consists of laboratory values captured in daily practice (measures of renal, hepatic, and hematologic function), as well as markers of inflammation and coagulation (IL-6, CRP, and D-Dimer), and the potential molecular marker of aging (p16\textsuperscript{INK4a} expression). These labs are drawn “pre-chemotherapy” and at the end of treatment (Procedure described in Data Management, 9.1.2.).

**6.5.1. Laboratory Values Captured in Routine Practice (Appendix I):** Laboratory values that are considered standard of care will be abstracted from the patient’s chart: hematologic function (WBC, hemoglobin, platelets), renal function (BUN, creatinine), and hepatic function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, alkaline phosphatase, albumin). The normal range for the particular lab value will be captured. A creatinine clearance will be calculated.

**6.5.2. Markers of Inflammation and Coagulation:** The Clinical Immunobiology Correlative Studies Lab at City of Hope will serve as the central laboratory for IL-6, CRP, and D-Dimer. Standard operating procedures for the collection of blood samples in EDTA-treated (lavender or pink top tubes, and a total of 10ml blood) for IL-6, CRP, and D-Dimer will be reviewed during the start up meeting (see 11.2.1. Training Procedures). D-Dimer will be analyzed using the IMUCLONE™ D-dimer ELISA kit from American Diagnostica Inc. CRP will be analyzed using the Procarta CRP Single Plex Assay Kit by Luminex®. IL-6 will be analyzed using the IL-6 Human Singleplex Bead Kit by Luminex®.

**6.5.2.a. Procedure for Processing Blood to Plasma:** The 10 mL of blood should be processed within 4 hours of collection. While awaiting processing, we recommend keeping the blood on a slow rocker if possible to mimic circulation and avoid clot formation. Within 4 hours of collection, the blood samples will be centrifuged at 1000g for 10 minutes. The plasma will be collected from the top, without disturbing the cell pellet. The plasma will be filtered by using a 5ml syringe to push through a 0.2 micron disposable filter unit (Acrodisc 25mm syringe filter with 0.2µm super membrane Pall LifeSciences Catalog No. 4612 or equivalent). The filtered plasma will then be divided into six equal aliquots (from 150 microliters to a maximum of 1ml per aliquot, depending on available plasma volume) in six 1.5ml microfuge tubes (Starstedt 72.692.005 or equivalent) and frozen in a -80°C freezer. The tubes of plasma should be labeled with patient ID number, date and time of blood draw, institution, and the volume of plasma. The plasma will remain stored in the freezer until it is time to be shipped. It is very important to avoid any freeze-thaw cycles.

**6.5.2.b. Specimen Shipping:** The plasma specimens will be shipped via Fedex Priority Overnight® on dry ice to ensure the specimens remain frozen during transportation.

Every 4 months, plasma specimens will be shipped (with the sample receipt form – Appendix V) from participating sites to:

City of Hope:  
Attention: Vivi Tran, CICSL Core Laboratory, Shapiro Bldg, Rm 1044, Beckman Research Institute of the City of Hope  
1500 E. Duarte Road  
Duarte, CA 91010-3000.  
Tel 626-256-4673 ext 62634.  
vtran@coh.org

**6.5.3. p16\textsuperscript{INK4a} Expression:** The measurement of p16\textsuperscript{INK4a} expression will be performed by Dr. Norman Sharpless’ laboratory at the University of North Carolina. The measurement of p16\textsuperscript{INK4a} expression will be performed in peripheral blood T lymphocytes by Dr. Sharpless’ lab.

**6.5.3.a. Procedure for Processing Blood for p16\textsuperscript{INK4a} expression:** Draw at least 6 ml blood in 10 mL heparin treated (green top) tubes. This 6mls of heparinized whole blood will be split between three 15mL conical tubes. Histopaque 1077, PBS/2% FBS, and RosetteSep Human T Cell Enrichment Cocktail will be brought to room temperature (15-25°C). RosetteSep Human T Cell Enrichment Cocktail will be added to each conical tube at a volume of 50uL per 1mL of whole blood. Tubes will be mixed well and then incubated for 20 minutes at room temperature. Samples will be diluted with...
PBS/2% FBS according to volumes shown in Table 1. Diluted samples will then be mixed gently. The diluted sample will be layered on top of Histopaque 1077 with extra care not to mix density medium and sample. Tubes will then be centrifuged at 1200 x g for 20 minutes at room temperature with no brake. Enriched cells will be removed from the plasma interface using a pipet. Some of the density medium will be collected with the enriched cells to ensure complete recovery. The enriched cells will then be placed in 15 mL conical tubes. The cells will be washed by adding PBS/2% FBS to the tubes until they are filled to the top fill line. The tubes will then be centrifuged at 400 x g for 4 minutes at room temperature with no brake. The supernatant will be removed with a pipet and the pellet will be resuspended. The cells will be washed again by adding PBS/2% FBS to the top fill line and then centrifuging the tubes at 400 x g for 4 minutes with maximum brake. Again the supernatant will be removed via pipet. The pellet will be resuspended by adding 0.5 mL PBS/2% FBS to each tube. The tubes will be mixed well and then combined before being transferred to a 2 mL cryovial. The cryovial will then be centrifuged at 1900 x g for 4 minutes at room temperature with low brake. The supernatant will then be removed with a pipet until the pellet is thoroughly dry. After removal of the supernatant, the sample will be placed in a -80°C to freeze down the cell pellet. The sample can be stored in the freezer until it is ready for shipment. Separately an aliquot of 500 uL of whole blood should be collected from either the Heparinized tubes or the EDTA-treated tubes and transferring into a 2 mL cryovial for future DNA isolation. Quick freeze this sample by placing in a -80°C freezer. The sample can be stored in the freezer until it is ready for shipment.

6.5.3.b. Specimen Shipping: Every 4 months, cell specimens and frozen whole blood will be shipped from participating sites (including City of Hope) to Dr. Sharpless’ laboratory at the University of North Carolina. The cell specimens will be shipped via Fedex Priority Overnight® on 12 lb of dry ice to ensure the specimens remain frozen during transportation.

| Table 1: Dilution of Whole Blood and RosetteSep Human T Cell Enrichment Cocktail |
|------------------|-----------------|-----------------|-----------------|-----------------|
| Whole Blood (mL) | PBS/2% FBS (mL) | Density Medium (mL) | Tube Size (mL) |
| 2                | 2               | 3               | 15              |
| 3                | 3               | 3               | 15              |
| 4                | 4               | 4               | 15              |

6.6. Assessment of Toxicity (Appendix III): Chemotherapy toxicity will be captured in a standardized manner using the NCI Common Toxicity Criteria for Adverse Events (v4.0). The research assistant or nurse will be present at each scheduled doctor’s visit where chemotherapy toxicities are captured and graded. The medical record will also be reviewed in order to capture each clinical encounter (scheduled or emergency visits). This will include a review of the clinic notes, emergency room visits, and hospitalizations. If the patient seeks emergency care outside of the primary institution, the patient’s permission will be obtained to review these outside records. Each patient’s clinical course will be reviewed by 2 physicians. For patients accrued at one of the collaborating institutions outside the City of Hope, the clinical course will be reviewed by the national PI (Hurria) and site PI. For patients accrued at the City of Hope, the clinical course will be reviewed by Dr. Hurria (national PI and site PI for City of Hope) and the patient’s treating...
oncologist. Toxicity reviews will occur via a conference call including the 2 physicians, the project manager, and the site research assistant or nurse. These conference calls will take place twice a month. During the conference calls, the medical record will be reviewed and grade 2-5 toxicities (NCI CTCAE v4.0) attributable to the chemotherapy course will be captured. Details regarding the overall category of toxicity (hematologic or non-hematologic), specific type of toxicity, and the rationale for the toxicity grade will be captured. Hospitalizations, dose reductions, dose delays or discontinuation of the chemotherapy course will also be captured, as well as the cause (ie, relationship to toxicity). A final “toxicity tool” (Appendix III) will be completed for each patient summarizing the above.

6.7. Relative Dose Intensity (Appendix III): The chemotherapy type, dosing, and schedule (intended and actual received), and supportive care medications will be abstracted from the chemotherapy orders, medical, and pharmacy records. The planned adjuvant chemotherapy regimen will be classified as “low,” “intermediate,” or “high” intensity based on the National Comprehensive Cancer Network (NCCN) guidelines, which groups regimens into low, intermediate, or high risk based on the risk of fever and neutropenia. For regimens not listed in these NCCN guidelines, the expert opinion of the 7 co-investigators, who are oncologists, will be used to develop a consensus regarding the classification of chemotherapy intensity. Hospitalizations, dose reductions, delays, or discontinuation of treatment will be captured, and the reasons for each of these outcomes. The cumulative dosages per unit time of the individual drugs in the regimen will be calculated: (total mg of drug in all cycles/m² body surface area)/ (total days of therapy/7). The actual dose delivered (numerator of RDI) will account for chemotherapy dose reductions. The denominator is based on total days of treatment (day 1 of cycle 1 through 1 cycle length after the date of the last treatment), reflecting all dose delays. The RDI is calculated as the ratio of the amount actually delivered to the amount intended based on standard guidelines. The RDI is calculated for each cytotoxic drug in a multidrug regimen, averaged to derive the overall RDI.

6.8. Survival Status (Appendix IV): Patients will remain on study while they are receiving the specified chemotherapy course up until 1 month following completion or discontinuation of treatment. Patients will then be followed in order to collect date of death information. All patients enrolled on the study will be asked to provide consent stating that their medical condition would be followed indefinitely and survival data would be gathered. In addition, they have consented to give authorization to use and disclose protected health information for the purposes of this study. The investigators will utilize the Social Security Death Index and the National Death Index to establish survival status. In order to obtain survival status on the enrolled patients we will need the patient's first and last name, middle initial, social security number, date of birth, and gender. This information will be securely transferred to the primary coordinating institution (City of Hope) and will be kept in a separate password protected file, which will only be linked for the purpose of establishing survivor status.

7.0 STUDY METHODS AND RECRUITMENT PLAN

7.1. Subject Identification and Recruitment
Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team. If the investigator is a member of the treatment team, s/he will screen their patient’s medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study. The study staff will request permission by the treating physician prior to approaching a potential subject.
During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes. Demographic information will be collected on any subjects that decline enrollment in this trial in order to determine whether there are different demographic characteristics among patients who decline the protocol or agree to participate.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator, or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable). Demographic information will be collected on any subjects that opts to refuse enrollment in this trial in order to understand if there are differences in participants and non-participants.

8.0 TOXICITIES/SIDE EFFECTS

8.1. Potential Risks to the Research Subjects:

Participation in this study does not entail physical or medical risks that are in and of themselves greater than those ordinarily encountered in daily life. The clinical and biological assessment (See Appendix I & II) will consist of questions relating to sociodemographic, tumor and treatment, and geriatric assessment variables, as well as laboratory values obtained through blood work. It is possible that the participant may feel uncomfortable if he/she has difficulty answering a question. If a patient becomes upset by the study questions, the site PI will talk with the patient either at the time of the interview or will contact the patient by telephone, in collaboration with the patient’s primary physician or designated coverage. If any further referrals are deemed necessary (i.e. social work and/or psychiatry), these referrals will be made in collaboration with the patient's primary medical team. The results of the assessment questionnaires and the toxicity tool will be available for the patient’s primary physician to review. The interview can be discontinued at any time and patients may refuse to answer any questions they find upsetting and do not wish to answer. If the patient wishes, he/she may decline participation in any part of the study or choose to discontinue participation in the protocol at any timepoint. As a part of the informed consent, we will specifically state that choosing not to participate in this protocol will not affect the patient's medical treatment in any way.

Although there is the potential for distress while completing the patient questionnaire, our experience with 500 patients enrolled on the Cancer and Aging Research Group Study 06170 (which used the same clinical assessment) has found this to be a rare event.

Every attempt will be made to draw the research blood at a time when the patient is engaging in a blood draw as part of the standard of care in order to decrease the need for additional venipuncture. There are limited risks associated with phlebotomy, including: bruising; minor pain or discomfort comparable to a needle prick; and rarely, infection. We expect that participation in this study will pose no additional physical risk to the patient other than a small risk of bruising or negligible risk of infection at the site of phlebotomy.

While there are no direct financial costs for taking part in this study, we recognize the patients are donating their time for participation. Patients will not be compensated for their participation.

As with any collection of individually identifiable health information there is a risk of breach of confidentiality. However, adequate safeguards will be in place to ensure that these risks are minimized. The study
database will hold strictly de-identified data using an arbitrary participant ID; paper forms will be stored in a secure location and referenced only for scheduling contacts; and a bridging table associating the two entities will be stored in yet another secure location. Upon initiating the study, all data will be collected and processed using rigorous quality-control methods.

8.2. Potential Benefits to the Research Subjects:
While there are no direct benefits to the participant, we hope that the knowledge we learn from this study will be instructive and beneficial to physicians and patients, provide insight into the factors influencing the trajectory of adjuvant therapy, and lead to further educational efforts and interventions to improve the care of this patient population. The results of this research will be presented and published.

8.3. Alternatives:
Participation in this study is voluntary. Participants may choose to participate or decline. There are no adverse consequences to not participating.

8.4. Confidentiality:
The study protocol will strictly adhere to all HIPAA and COH IRB regulations. Confidentiality of the subjects will be maintained. No data will be linked to a particular name or personal identifiers. The individual results will not be disclosed. The de-identified dataset will be provided to the investigators for analysis. The composite results will be analyzed and summarized for presentation and publication.

8.5. Financial Compensation and Obligation to be Incurred by the Research Subject:
The participant will be no compensation for participating in this study.

8.6. Informed Consent Process:
Ethical standards for human subjects will be strictly followed. After obtaining permission from the primary treating clinician, patients who meet the eligibility criteria will be approached and recruited for this study by the site PI or another trained member of the research team. All investigators and research assistants will have undergone full training in Human Subjects Protection Certification. In addition, all research team members will undergo formal training regarding the research procedures, including the informed consent process. Once initial contact has been established, the site PI or their trained research staff will present the study to potential participants, strictly adhering to ethical and regulatory standards for human subjects research. The purpose, procedures, duration, risks, and alternatives of the study will be thoroughly explained to potential subjects. It will be emphasized that participation is completely voluntary and that patients may choose to withdraw at any time without adverse consequence to their medical care or loss of benefits to which they are otherwise entitled. Patients will be informed of the research nature of this project and that while their participation may enable improvements in patient care, this project is not designed to benefit them individually. Extent of confidentiality provided and procedures for protecting confidentiality will be discussed in specifics, such as the need to review medical records to confirm cancer treatment and laboratory data. Informed consent will be contingent upon the patient’s full awareness and affirmation of these ethical standards. Once all questions have been addressed and the individual indicates he/she would like to participate, signed informed consent and HIPPA Privacy Rule Authorization will be obtained. Individuals who are unable to provide informed consent will be excluded from participation in the study. A consent document will be signed and maintained in the participant’s medical record. Two additional copies of the consent form will be made. One copy will be given to the patient at the time of consent and the other copy will be kept in the research record. Children will not be included in this study (the study will enroll individuals age 65 and older) so parental permission is not an issue.

With patient permission obtained (via informed consent), leftover mRNA and DNA samples obtained from the research blood will be stored within the Cancer and Aging Centralized Biological Specimen Bank in the Translational Research Core at City of Hope in order to be banked for future research. Such studies might include genetic testing to determine how genetics influences chemotherapy toxicity. The specific risks and benefits of characterization of $p16^{INK4a}$ expression and potential future genetic studies will be discussed in detail in the informed consent. If the subject agrees to allow their specimens to be used for future research, he/she may change their mind at any time and may withdraw their informed consent for the use of
specimens for future research as detailed in the consent form. Once the PI or site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

With IRB approval, we will obtain permission from subjects who decline participation in the study to record their stage, gender, age, race, ethnicity and reason for their refusal. No other information will be recorded. This information will allow the study team to determine whether specific patient characteristics are associated with willingness to enroll and whether modifications to the recruitment process are warranted.

9.0 REGISTRATION GUIDELINES AND DATA MANAGEMENT

9.1. Data Management and Quality Assurance:

9.1.1. Training Procedures: The PI, assisted by the project manager at City of Hope (COH), will ensure that all co-investigators and their research teams are trained in the research procedures. A start-up meeting will be held during the 1st year of the grant. All participating investigators will undergo training in human subject protection. The research study staff will undergo centralized training with the project manager which will include a detailed review of the study rationale, design, and research administration procedures (to be summarized in a field manual). The training procedure and field manual will review the following procedures: 1) informed consent; 2) completing the geriatric assessment (Appendix I and II); 3) data collection via chart extraction (for Appendix I, III, IV); 4) transfer of the data to COH; 5) formulating the research chart; 6) collection and shipment of blood (markers of inflammation and coagulation) to City of Hope; 7) collection and shipment of blood to Dr. Sharpless’ lab for p16<sup>INK4a</sup> expression; 8) competency training (utilizing the Multicultural Tool Kit<sup>140</sup> developed by the Oncology Nursing Society); and 9) a discussion of interviewing techniques so that the research team will standardize their approaches in order to elicit consistent data from subjects.

9.1.2. Data Management: COH will be the coordinating center for data entry. Dr. Hurria’s team served this function in the national prospective cohort study, CARG Study 06170. At each site, a HIPAA compliant local administrative tracking system will be used to monitor patient follow-up schedules, accrual, and refusal rates. The study team has already created data collection forms (Appendix I-IV). Once the patient consents to the protocol, he/she will be assigned an encrypted patient identifier number to be used on all patient data forms. The study database will hold strictly de-identified data using the participant ID. Upon initiating the study, all data will be collected and processed using rigorous quality control methods. Within 72 hours after the research assistant completes the data collection (Appendix I and II), these de-identified data will be sent via fax to the project manager at COH. At each study site, a log of faxed forms will be maintained, with lists of faxed forms e-mailed via secure e-mail to the project manager at COH. The data will be entered into the secure access de-identified database within 72 hours of receipt at COH. All data entered into this database will be double-checked by a 2<sup>nd</sup> research assistant. The initials of the individuals who entered and double-checked the data are recorded in the database. The research assistant will check Appendix I and II prior to faxing the data to COH in order to reconcile any missing data (or to provide an explanation as to why data are missing). When the data arrive at the COH, the research assistant at COH will do a 2<sup>nd</sup> check to make sure that all data are complete. The blood specimens (IL-6, CRP, D-Dimer, and p16<sup>INK4a</sup>) will be labeled with the patient ID number, date and time the blood is drawn, and the institution that drew the blood. The blood specimens drawn for markers of inflammation and coagulation (IL-6, CRP, D-Dimer) will be spun down by the collecting site to plasma (See procedures described in 6.5.2. Markers of Inflammation and Coagulation). A shipping log will be kept at each institution specifying the date and time the specimens were shipped and the date and time that the receipt of the specimen was confirmed. This shipping log will be faxed to COH every Monday where a combined shipping log of all of the specimens will be kept. These shipping logs will be reviewed during the study team conferences calls (described below). City of Hope will maintain a secure, de-identified database with the IL-6, CRP, and D-Dimer results. Dr. Sharpless will maintain a secure, de-identified database with the p16<sup>INK4a</sup> results. These data will be securely transferred to COH.

Conference calls are to be twice a month with each participating site. These calls include: 1) the national study PI (Dr. Hurria); 2) project manager; 3) site PI; and 4) site research assistant. During these calls, study reports (accrual/retention, received data, etc) will be reviewed. A systematic review of each patient’s chart will be performed to capture grade 2-5 toxicity attributable to chemotherapy, hospitalizations,
dose delays, dose reduction, and reason for discontinuation of chemotherapy. Based on this team’s experience from CARG 06170, on average, 6 patient charts can be reviewed in a 1-hour conference call. These data will subsequently be summarized in a toxicity tool (Appendix III) and entered into a password protected access database, stored on the secure server at COH. These data will be backed-up every 24 hours. No personally identifying information will be used in any publications that result from this study.

Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study. To register a patient, the research nurse or CRA must complete the Eligibility Checklist. The research nurse or CRA will register the patient onto the study and assign a patient accession number. Registration will be done at City of Hope.

Patient Consent Form: At the time of registration, three signed and dated copies of the patient Informed Consent form and the Experimental Subject’s Bill of Rights for Treatment Studies must be available for the patient, the patient's medical chart and the research record.

10.0 DATA SAFETY AND MONITORING PLAN

10.1. Definition of Risk Level:
This is a Risk Level 1 study, as defined in the “Guidance, Policy and Procedures for Data and Safety Monitoring for In-House Trials at City of Hope”, http://www.infosci.coh.org/ocrqa/forms/guidance.doc, because it involves blood draws and questionnaires, where the risk of harm is low.

10.2. Monitoring and Personnel Responsible for Monitoring:
The Principal Investigator is responsible for monitoring protocol conduct and reporting to the COH DSMB any adverse events related to study procedures.

10.3. Adverse Events Reporting:
Any unanticipated AE requires reporting if it is related to the clinical or biological assessments done for this protocol. Adverse events and/or unanticipated problems must be reported to COH DSMB and IRB according to definitions and guidelines at http://www.infosci.coh.org/ocrqa/forms/guidance.doc and http://resadmin.coh.org/doc/irb3810.doc.

11.0 BIOSTATISTICS

Specific Aim #1: To develop a predictive model of clinical and biological predictors for grade 3-5 toxicity to adjuvant chemotherapy: We will use logistic regression to develop a predictive model for the occurrence of any NCI CTAE (v4.0) grades 3-5 toxicity, and validate the model internally. Two models can result consisting of: 1) solely clinical and routine laboratory variables; and 2) clinical and routine laboratory variables and biomarkers of aging. A total of 29 variables will be considered: 4 sociodemographic (age, race/ethnicity, education, marital status); 4 tumor and treatment factors (tumor stage, chemotherapy regimen intensity, surgery type, radiotherapy); 5 routine laboratory measures (creatinine clearance, abnormal liver function, WBC, hemoglobin, platelets); 12 geriatric measures; and 4 biological markers of aging (IL-6, CRP, D-Dimer, p16INK4A). We will use all 500 patients, initially entering all relevant covariables in the model and applying step-wise backward elimination to obtain the final model containing only the significant (P<.01) predictors. A more stringent type I error (0.01) will be used to avoid over-fitting. The first model will be developed by considering the first 25 variables, and the second with all 29 variables. Goodness-of-fit will be examined by Hosmer-Lemeshow test. The predictive performance will be assessed by the area under the curve (AUC) in the receiver operating characteristic curves. An AUC=0.5 indicates the predictability to be no better than a random guess. Since the apparent AUC is overoptimistic, a 10-fold cross validation will be performed to calculate mean AUC to obtain a less biased estimate of the predictive accuracy. We will also assess the model calibration. A well-calibrated model has a straight-line relationship between predicted probabilities and observed probabilities, with 0 for intercept and 1 for slope. Deviation from this linear relationship can be tested with a likelihood ratio test. Shrinkage factors will be estimated to re-calibrate the coefficients in the models. A prediction model with only clinical and routine laboratory measures will be useful as it requires no extra effort to obtain the currently non-routinely measured biological markers of aging. If a prediction model that includes biological
markers of aging also results, we will compare it against the model without the markers for expected AUC, optimism, and calibration. If the overall amount of missing data is <10%, we will perform case deletion. Otherwise, an imputation strategy will be used for missing covariates. Logistic regression will be conducted using PROC LOGISTIC (SAS Institute, Cary, NC) and 10-fold cross validation will be conducted using a SAS macro.

Specific Aim #2: To understand the associations between clinical and biological factors and reduced RDI of the prescribed chemotherapy regimen: RDI will be treated as a continuous and a dichotomous variable (RDI<85% vs RDI ≥85%). The distribution of continuous RDI will be examined graphically and transformed to normality as appropriate. Linear regression for continuous RDI and logistic regressions for dichotomized RDI will be performed to elucidate the relationship with the 29 independent variables. Stepwise regression will be used to identify the significant clinical and biological factors and biological markers of aging that are independently associated with continuous RDI and dichotomized RDI.

Specific Aim #3: To identify the specific chemotherapy toxicities associated with decreased RDI of the prescribed chemotherapy regimen: Toxicities will be divided into hematological and non-hematological types. For each type, the number of patients who experience decreased RDI due to 1) dose reduction, 2) delays, and 3) early discontinuation will be tabulated. For each reason for decreased RDI, the specific adverse events that affected dose alteration will be tabulated. Chi-square test of homogeneity will be conducted to examine variation in frequencies by toxicity type.

11.1. Power and Sample Size Calculations

Specific Aim #1: To develop a predictive model of clinical and biological predictors for grade 3-5 toxicity to adjuvant chemotherapy: A statistical rule of thumb for sample size for developing a predictive model requires at least 10 events per predictor variable (EPV) considered; 142, 145 which may be conservative. 146 With this guideline in mind, we powered the study to: 1) identify statistically significant sociodemographic and clinical variables, and biological markers of aging as predictors of grade 3/4/5 toxicity; and 2) obtain reasonably accurate confidence intervals (CI) for odds ratios (OR) of the predictors. The prevalence of any grade 3/4/5 toxicity among breast cancer patients ≥65 is 50% based on previous publications4, 67, 120 and the 38 breast cancer patients on adjuvant chemotherapy in the CARG Study 06170 (see Section 3.7.4). This is also reasonable for patients age > 70. We expect 250 patients to develop grade 3/4/5 toxicity, thus EPV=9 (250 events/29 variables). With EPV=5-9, problems with CI coverage < 93%, type I error >7%, or relative bias >15% associated with predictive model development are uncommon. 146 For model validation, with AUC=0.5 being no better than a random guess, 500 patients will detect AUC ≥0.57 at type I error=0.01 and power=0.80. Applying the predictive model in CARG Study 06170 to 210 patients in the data who received adjuvant chemotherapy gave AUC=0.66, with largest OR=2.2 (95% CI: 0.9-5.5) for “at least 1 fall in the last 6m” and smallest OR=1.3 (95% CI: 0.6-2.6) for “needing assistance”. For a 2-sided test and type I error=0.01, 500 patients in whom 30% are in the group x=0 and 50% are in the group x=1 for a binary predictor x, power will be 80% to detect OR=1.8 to 3.1 for the prevalence of grade 3/4/5 toxicity ranging from 0.05 to 0.5 in the x=0 group. We assumed near zero correlation between the predictor and covariates already in the model.

For biological markers of aging treated as normally distributed continuous variables, the prevalence of any grade 3/4/5 toxicity ranging from 0.10 to 0.45 at the mean level of this marker, 500 patients will provide 80% power to detect a prevalence difference of 0.05 to 0.08 (OR=1.4 to 1.7) when the biomarker level is increased by one SD above the mean, assuming a 2-sided test, a type I error=0.01, and a correlation of 0.3 between the biological marker and other covariates in the predictive model. For larger correlations, larger differences in prevalence rates are required. However, with a correlation as high as 0.6, 500 patients should provide 80% power to detect a prevalence difference of 0.10 to 0.12 or OR=1.6 to 2.2.

A shorter confidence interval is desirable for more accurate risk estimation. "MOS Social Activity score ≤50 vs ≥50" was also included as a significant predictor in the model estimated from 500 patients in CARG 06170. When the model parameters were re-estimated for 210 patients undergoing adjuvant chemotherapy, adjusted OR was 1.9 with 95% CI of 0.8 - 4.1 (width =3.3). Assuming 1.9 as the true underlying OR and equal sample size in the two groups defined by a binary predictor, 500 patients will narrow the 95% CI to 1.12- 3.18 (width=2.06) for prevalence rate=.10 and to 1.32-2.71 (width=1.39) for prevalence rate=0.50 in the referent group, achieving a reduction in CI width of 37% to 58%.

Specific Aim #2: To understand the associations between clinical and biological factors and reduced RDI of the prescribed chemotherapy regimen: As described earlier, 500 patients (in which 50% are in the group
Based on this team's experience from CARG 06170 (3.7.4), on average, 6 patient charts can be reviewed in calls, study reports (including study PI (Dr. Hurria); project manager; site PI; and site research assistant). The results will be entered into the secure access database maintained at COH, with lists of faxed forms mailed via secure email to the project manager at COH. Upon initiating the study, all data will be collected and processed using rigorous quality control methods. Upon initiating the study, all data will be collected and processed using rigorous quality control methods. Within 72 hours after the research assistant completes the data collection (Appendix I and II), these de-identified data will be sent via fax to the project manager at COH. At each study site, a log of faxed forms entered into this database will be double-checked by a 2nd research assistant. The initials of the individual who entered and double-checked the data are recorded in the database. The research assistant will check Appendix I and II prior to faxing the data to COH in order to reconcile any missing data (or to provide an explanation as to why data are missing). When the data arrive at the COH, the research assistant at COH will do a 2nd check to make sure that all data are complete. The plasma (IL-6, CRP, D-Dimer) and blood specimens (p16INK4a) will be labeled with the patient ID number, date and time the blood is drawn, and the institution that the blood was drawn at. A shipping log will be kept at each institution specifying the date and time the specimens were shipped and the date and time that the receipt of the specimen was confirmed. This shipping log will be faxed to COH every Monday where a combined shipping log of all of the specimens will be kept. These shipping logs will be reviewed during the study team conferences calls (described below). City of Hope will maintain a secure, de-identified database with the IL-6, CRP, and D-Dimer results. Dr. Sharpless will maintain a secure, de-identified database with the p16INK4a results. These data will be securely transferred to COH.

Conference calls are to be twice a month with each participating site. These calls include: 1) the national study PI (Dr. Hurria); 2) project manager; 3) site PI; and 4) site research assistant. During these calls, study reports (acquisition/retention, received data, etc) will be reviewed. A systematic review of each patient's chart will be performed to capture grade 2-5 toxicity attributable to chemotherapy, hospitalizations, dose delays, dose reduction, and reason for discontinuation of chemotherapy (procedure described in 6.6.). Based on this team's experience from CARG 06170 (3.7.4), on average, 6 patient charts can be reviewed in
a 1-hour conference call. These data will subsequently be summarized in a toxicity tool (Appendix III) and entered into a password protected access database, stored on the secure server at COH. These data will be backed-up every 24 hours. No personally identifying information will be used in any publications that result from this study.
REFERENCES


