Chemotherapy Related Cognitive Impairment

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School of Nursing
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Abstract

of

CHEMOTHERAPY RELATED COGNITIVE IMPAIRMENT

by

Jamila Faiq

Little is known about cognitive impairment related to chemotherapy. Patients who receive chemotherapeutic drugs report cognitive impairment during or subsequent to treatment (Raffa, 2010). It is vital to determine the short-term and long-term consequences of cognitive change related to chemotherapy and its impact on quality of life. A great need exists for research focused on the effects of high dose chemotherapy on cognitive function. In addition, large-scale prospective clinical trials with longitudinal design and appropriate controls to evaluate the probability of chemotherapy related cognitive impairment are needed. Currently, there are no reported studies that have investigated the effects of high dose Melphalan on cognitive function for individuals with multiple myeloma in the setting of a stem cell transplant.

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Chapter One: Introduction

Background

Chemotherapeutic drugs have contributed to substantial improvements in the survival of cancer patients. However, such drugs have adverse effects that can be debilitating and even life-threatening. One adverse effect is “chemo brain;” a very poorly understood but a well-documented phenomenon. Chemo brain refers to the cognitive deficits that are experienced by some individuals during and following chemotherapy (Staat & Segator, 2005).

Further, Rodin (2012) pointed out that the term “chemo brain”, which is sometimes also called “chemo fog”, originated from cancer support groups to describe the experience of vaguely defined impaired cognitive functioning that many individuals reported. The chemo brain phenomenon has been more formally termed “Chemotherapy-Related Cognitive Change” (Kanskie, 2012) but has also been referenced as “Chemotherapy-Related Cognitive Impairment” (Becze, 2012; Raffa, 2010; Meyers, 2008), “Chemotherapy-Induced Cognitive Impairment” (Evens & Eschiti, 2009) and “Chemotherapy-Associated Cognitive Impairment” (Raffa, 2013).

Although cognitive change related to chemotherapy has been documented as early as 1980 by psychiatrists, it has only recently been addressed consistently in the literature (Kanaskie, 2012; Myers, 2008). Many studies have explored different mechanisms for this phenomenon and resulting in a variety of postulations. Evens & Eschiti (2009) suggest that cognitive impairment related to chemotherapy is a result of alterations in the blood-brain barrier, vascular injury and myelination changes and may have a genetic link.
Other studies have pointed to potentially associated factors such as patients’ age, educational level, fatigue, depression, anxiety, disease site and stage, other comorbidities, and treatment regimen. (Myers, 2008). Several mechanisms of cognitive impairment have been proposed; however, experimental research to identify cause and effect relationships has been difficult because of the inability to study comparison groups and control for confounding variables (Hafner, 2009).

Consequently, the causative role of chemotherapy in producing the cognitive impairment is not fully understood and there remains a lack of conceptual definition of cognitive change related to chemotherapy (Kanaskie 2012; Rodin 2012). Chemotherapy-related cognitive change is described as dysfunction, weakening or impairment of memory in patients who have been treated with chemotherapy (Staat & Segatore, 2005). Becze (2012) defines cognitive impairment as “chemotherapy-related changes in the brain that affect a patient’s ability to think, concentrate, formulate ideas, reason, and remember.”

Kanaskie (2012) presented the results of a principle-based concept analysis of cognitive change in patients with cancer following chemotherapy treatment. She proposed a theoretical definition reflecting the current state of the science as the final product of her principle-based concept analysis. She defines chemotherapy-related cognitive change as a “multidimensional phenomenon that follows cancer diagnosis and chemotherapy treatment and involves the patient’s perception of change in his or her cognitive abilities” (p. E242).
The impact of chemotherapy-related cognitive impairment is typically subtle and limited (Myers, 2008) and can be viewed as insignificant compared to the potentially life-saving benefits of chemotherapy when faced with a life-threatening diagnosis of cancer (Evens & Eschiti, 2009). However, cognitive impairment can have a substantial impact on patients and their families. The cognitive functions that are most often affected include executive function, information processing speed or reaction time, verbal and visual memory, attention, concentration, language, motor skills, spatial skills, multitasking and ability to organize information (Raffa, 2010; Myers, 2008). Executive function includes attention regulation, planning and initiation of purposeful activity, anticipation of the consequences of one’s actions, problem solving and inhibition of inappropriate activity (Myers, 2008).

Patients may experience a constellation of cognitive deficits such as forgetfulness, absentmindedness, and an inability to focus when performing daily tasks (Hess & Insel 2007). These changes can negatively affect a person’s life and can result in the inability to resume attendance at school, work, or social activities, or make it extremely difficult to do so (American Cancer Society, 2012). This phenomenon can affect multitasking skills, create stress and weaken performance in the face of high-level cognitive demands (Staat & Segatore, 2005).

Individuals experiencing cognitive decline are usually aware of the changes and feel frustrated and helpless which increases the emotional burden of the diagnosis of cancer. It is difficult to predict which individuals will experience cognitive impairment secondary to cancer treatment. In those who are affected, severity and duration can be highly
variable and can be experienced as early as the first course of treatment or can result after several cycles of chemotherapy (Hafner, 2009). Although the effects of chemotherapy on cognitive function may be subtle, they may be severe enough to interfere with a patient’s daily functioning and quality of life (Evens & Eschiti, 2009).

Problem Statement

Presently, there is not a standard measurement or assessment of cognitive function in individuals with cancer nor are there established treatments available for patients who present with cognitive complaints (Hess & Insel, 2007). Some studies have demonstrated a lack of correlation between patient self-report of cognitive dysfunction and consequent performance on neurocognitive tests (Wefel et al., 2004; Evens & Eschiti, 2009). Additionally, the selection of neuropsychological tests used to measure cognitive change related to chemotherapy lacks consistency (Raffa, 2009) and currently no standardization of neuropsychological tests for this specific population has been established. Another issue regarding understanding the phenomenon of cognitive impairment due to chemotherapy is that it can resolve shortly after termination of chemotherapy in some patients but can last for months to years after treatment in others (Mitchell & Tunton, 2011; Evens & Eschiti, 2009).

Despite the increasing attention and research done to gain an understanding of cognitive impairment related to chemotherapy, little is known about this adverse effect. Some patients who receive cancer chemotherapeutic drugs report cognitive impairment during or subsequent to treatment while others do not and standardized tests detect these deficits in cognitive ability of some cancer survivors but not all (Raffa, 2010). It is not
known why certain patients experience cognitive deficits or why it persists in some and resolves in others. Understanding the state of the science is imperative in determining the long-term consequences of cognitive change and its impact on quality of life.

One of the main areas of concern in the study of cognitive impairment related to chemotherapy is that most studies have been conducted in women with breast cancer. Much of the literature describes patients with breast cancer because of the good prognosis and survival time in this population allowing for evaluation of concurrent and long-term consequences (Myers, 2008). Although many contributions have been made to the understanding of the phenomenon by studying patients with breast cancer, the findings from this patient population may not be generalizable to a wide range of cancers (Rodin, 2012). The interpretation of study results has also been limited due to descriptive study designs, small sample sizes, presence of uncontrolled confounding variables and the post-treatment timing of evaluation (Mitchell & Turton, 2011). In addition, most of the research has focused on the effects of standard dose chemotherapy on cognitive function.

A great need exists for research focused on the effects of high dose chemotherapy on cognitive function. Large-scale prospective clinical trials with longitudinal design and appropriate controls to evaluate the probability of chemotherapy related cognitive impairment are needed. Additionally, the expansion of clinical trials to study other cancer diseases occurring in female and male patients are important (Myers, 2008). Currently, there are no reported studies that have investigated the effects of high dose melphalan on cognitive function for individuals with multiple myeloma in the setting of a stem cell transplant.
Significance and Innovation

The concept of impaired cognitive function related to cancer treatment is important to nursing as it pertains to understanding the experience of the phenomenon and the exploration of strategies to manage the change (Kanaskie, 2012). Problems related to cognitive function may be subtle and may not be objectively evident, thus making assessment difficult. Patients presenting with cognitive complaints need to be assessed to determine appropriate intervention. Symptoms associated with cognitive dysfunction can negatively affect one’s quality of life by interfering with daily routines and planning abilities (Hafner, 2009).

Another concern regarding chemotherapy-induced cognitive impairment relevant to nursing practice is that this potential side effect is generally not discussed as a potential adverse side effect with patients prior to the initiation of treatment. Many nurses are not prepared to educate patients and families regarding the potential development of cognitive impairment (Myers & Teel, 2008). Consequently, many patients are unaware of it and the impact it may have on their cognitive functioning (Evens & Eschiti, 2009).

Understanding the cognitive changes that may occur as a result of chemotherapy is imperative for care providers in order to manage, improve, or maintain functional ability in addition to supporting health-related quality of life.

Purpose of the Study

The purpose of the proposed research is to measure the incidence of cognitive impairment in adult myeloma patients receiving high-dose melphalan followed by
autologous stem cell transplant and investigate how these patients perceive their cognitive abilities overtime.

**Research Question**

The research question is “What is the incidence of chemotherapy related cognitive impairment, “chemo brain”, in adult myeloma patients receiving high-dose melphalan followed by autologous stem cell transplant. The second part of the research question is "How effectively can the FACT-Cog longitudinally measure cognitive changes and perceived quality of life in patients with multiple myeloma who are receiving high dose chemotherapy?"

**Research Variables**

The dependent variable in this study is cognitive function as measured by the self-reported FACT-Cog (Version 3). The independent variable is high-dose Melphalan (100-200mg/m^2).
Chapter Two: Literature Review

An estimated 13 million Americans are living with cancer and over 1.6 million new cancer cases were projected for the year 2013 (American Cancer Society, 2013). Multiple myeloma is an incurable malignancy of the plasma cells which accounts for around 13-15% of all newly diagnosed hematological disorders and around 1% of all cancers (Potrata, Cavet, Blair, Howe & Molassiotis, 2010). Multiple myeloma accounts for about 22,350 new cases of cancer each year (American Cancer Society, 2013).

Following a diagnosis of cancer, chemotherapy is usually the standard treatment and may be used in conjunction with surgery and radiotherapy. Although chemotherapeutic drugs can be lifesaving, they may also result in a variety of unwanted side effects, some debilitating and others life threatening. One of the associated side effects that is not well understood is the changes in cognitive functioning referred to as chemotherapy-related cognitive impairment, or “chemobrain” as it is referred to in the lay literature.

The subject of cognitive problems following chemotherapy have been gaining interest in research and are continuing to be studied in order to gain a better understanding of the phenomenon. When the impact of cognitive impairment related to chemotherapy is better understood, appropriate interventions can be developed to manage these changes and help individuals cope with cognitive changes. Chemotherapy related cognitive impairment is typically not discussed prior to the initiation of cancer treatment and many nurses are not prepared to educate patients regarding this potential side effect (Myers & Teel, 2008).
Jim et al. (2012) reported the findings from a meta-analysis of data about cognitive effects of chemotherapy accessed from 17 studies of 807 breast cancer survivors who were treated with standard-dose chemotherapy. The results indicated that individuals with breast cancer performed worse than non-cancer controls on tests of verbal ability and worse on tests of visuospatial ability compared with individuals with breast cancer treated without chemotherapy. In this meta-analysis, it was found that age, education, time since treatment did not moderate observed cognitive deficits in verbal ability or visuospatial ability, although the effect sizes were small. The results of this meta-analysis indicates that, on average, cognitive deficits in patients with breast cancer previously treated with chemotherapy are small in magnitude and limited to the domains of verbal and visuospatial ability (Jim et al., 2012).

Another meta-analysis conducted by Jansen et. al. (2005), examined neuropsychological effects of chemotherapy on patients with cancer. Nine of the 16 studies included in the meta-analysis looked at patients with breast cancer and assessed for cognitive deficits during treatment or soon after treatment. The majority of those assessed for cognitive impairment performed statistically significantly worse than individuals with normative data in the domains of executive function, information processing speed, verbal memory and visual memory. Compared to healthy controls, small, statistically significant deteriorations were found in language and verbal memory with patients treated with chemotherapy. This meta-analysis found no significant differences in patients treated with chemotherapy when compared with control patients treated with local therapy or with their own baseline scores suggesting that cognitive
impairment related with chemotherapy are small to moderate and may be dependent on the study methodology used (Jansen et. al., 2005).

A meta-analysis conducted by Falleti, Sanfilippo, Maruff, Weih and Phillips (2005) examined the neuropsychological effects of chemotherapy on women diagnosed with breast cancer who were currently undergoing treatment as well as those who had completed treatment three weeks or one year prior. This meta-analysis included data from five cross-sectional studies and one longitudinal study. For the cross-sectional studies, the cognitive domains of attention, memory, motor function, executive function, spatial ability and language except for “attention” showed small to moderate effect sizes (-0.18 to -0.51). The largest differences were seen in the domains of motor function (d = -0.51), spatial ability (d= -0.48), and language (d = -0.41). The effect sizes for each study were small to moderate (-0.07 to -0.50) and regression analysis detected a significant negative relationship between study effect size and the time since last receiving chemotherapy. For the longitudinal study included in this meta-analysis, effect sizes ranged from small to large (0.11 – 0.9) and indicated improvements in cognitive function from the beginning of chemotherapy to weeks to a year following the treatment.

Stewart et al. (2006) conducted a meta-analysis on the relationship between adjuvant chemotherapy treatment for breast cancer and cognitive dysfunction. The studies in this meta-analysis included those assessing cognitive function using neuropsychological indices in which patients with breast cancer were compared with either baseline data or controls. Stewart evaluated eight cognitive domains: simple attention, working memory, short and long-term memory, speed of processing, language,
spatial abilities and motor function. Of the eight cognitive domains evaluated, statistically significant small to medium weighted pooled effect sizes \((d = -0.22 \text{ to } -0.37)\) were found in all domains except for simple attention. Patients treated with chemotherapy performed worse in all domains with the largest differences observed in language and short-term memory. However, additional studies with similar results would be necessary to increase confidence in these results. Overall, the results indicated that women who receive chemotherapy for breast cancer may experience considerable cognitive decline.

**Measuring Cognitive Function**

Little or no change in cognitive ability on standard cognitive assessment instruments have been found despite self-reports of perceived cognitive changes by the study participants (Kanaskie, 2012). There is also an ongoing debate regarding which method of measurement is the gold standard for assessment of cognitive change related to chemotherapy: subjective self-report, objective neuropsychological evaluation or neuroimaging. Unfortunately, methodological difficulties in study designs have resulted not only in underestimating the magnitude of the problem, but even its existence (Raffa, 2009).

Recent studies have incorporated neuroimaging tests as a useful tool in identifying areas of the brain affected by chemotherapy and seek to provide a rationale for patient self-reports of cognitive impairment despite normal performance on the neurocognitive tests (Myers, 2008). Raffa (2009) has supported the use of neuroimaging techniques to address the inconsistency in the methods used to measure cognitive deficits. Neuropsychological testing in a twin study demonstrated similar results; however, the
twin who underwent chemotherapy for breast cancer reported problems with cognitive function and had markedly differing structural and functional MRI images. This suggests that physiologic mechanisms may be present in those who experience cognitive dysfunction post-chemotherapy, in the absence of impaired neuropsychological performance (Wagner et al., 2009).

**Effects of Chemotherapeutic Agents on Cognitive Function**

Very few studies have examined the relationship between chemotherapy and cognitive impairment in cancer patients other than those diagnosed with breast cancer. One study conducted by Potrata, Cavet, Howe, Blair and Molassiotis, (2010) explored cognitive impairments in patients with multiple myeloma in order to gain an understanding of cognitive impairments and concerns as described by the patients. This phenomenological qualitative study included 4 informants who were less than one year from diagnosis, two who were between 1-5 years from diagnosis and nine who were more than 5 years after their initial diagnosis. Eleven of the patients who accounted for 73.3% of the sample had received a stem cell transplant.

Subjective cognitive impairments such as poor recall, problems with short-term memory and lack of concentration were self-reported by 10 patients (66%). It was found that one of the frequent coping strategies patients employed to address the problem of poor short-term memory and concentration was denial. Overall, the research indicates that a considerable number of myeloma patients may suffer from bothersome cognitive difficulties affecting their personal and professional lives and that these changes can be permanent for some. The most severe problems with cognitive functions included those
patients who have undergone stem cell transplants alluding to the importance of research on the potential effects of stem cell transplantation.

Another study assessed for cognitive impairments in patients with lung cancer. Whitney et al (2008) reported the results of a pilot study which examined 14 stage III non-small cell lung cancer patients who received treatment with cisplatin, etoposide, and radiotherapy. Patients were evaluated with a comprehensive battery of examiner-administered cognitive tests and self-reported questionnaires before receiving chemotherapy and at one and seven months after treatment. The baseline assessment showed that 71% of patients (n=10) were judged to be cognitively impaired using the Hopkins Verbal Learning Test, a measuring verbal learning and memory (recognition and recall). This study looked at different variables that may impact the cognitive test scores such as laboratory values of TSH, homocysteine, or hemoglobin and found no statistically significant correlations.

One month post chemotherapy tests demonstrated a decline in cognitive function in 62% of the patients (n=8) with the most significant changes seen in the measure of conceptual flexibility but were also noted on all five other neuropsychological measures utilized in the study. Of the eight patients, two passed away and one dropped out leaving five patients to compare the 7-month evaluation to the initial one-month follow up. Although the sample size was small, the results indicated that cognitive declines were temporary. This study also found no statistically significant correlations between neuropsychological test results and mood ratings, fatigue ratings, quality of life variables, or age at any of the three assessment time points.
Cognitive complaints and impairment were also evaluated in patients with testicular cancer following bleomycin, etoposide, and cisplatin (BEP) chemotherapy. Schagen et al (2007) compared three groups of patients with testicular cancer: those who received chemotherapy after surgery, received radiotherapy after surgery, or received surgery only. The neuropsychological status of all patients was assessed using a standard battery of neuropsychological tests in addition to interviewing patients regarding cognitive problems, health-related quality of life, anxiety and depression, and fatigue.

Of the 182 patients included in the study, 70 received chemotherapy after surgery, 57 were treated with radiotherapy after surgery, and 55 received surgery only. Self-reported cognitive problems were equal between the surgery plus chemotherapy group and surgery plus radiotherapy group (32%) and 27% in the surgery only group. When assessing for the health-related quality of life, anxiety, depression and fatigue, no significant differences were found between the three groups except for the global quality of life scale in which the surgery plus radiotherapy group reported lower scores indicating a lower level of functioning. The study found that, the percentage of patients classified as neuropsychologically impaired in the surgery plus chemotherapy group remained significantly different from the surgery only group (p= 0.038) and from the surgery plus radiotherapy group (p=0.070). Furthermore, this study found no significant correlation between the overall cognitive impairment score and the occurrence of cognitive problems reported at the interview. This study suggests that the self-reported cognitive problems were related to the anxiety and depression scales of the Hopkins Symptom Checklist. The time since treatment was not found to influence the relationship
between the self-reported problems, or the relationship between self-reported problems and neuropsychological test results.

In many studies, neuropsychological tests used to evaluate cognitive problems objectively, did not appear to be sensitive enough to detect subtle changes related to chemotherapy treatments (Joly et al., 2012). Consequently, the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) scale (Appendix 3) was developed to address this void. Items on the scale were identified through qualitative analysis of interviews with expert oncologists and patients following chemotherapy. The scale demonstrated a high level of internal consistency reliability using Cronbach’s coefficient alpha (0.707–0.929) when pretested with cancer patients undergoing chemotherapy treatment (Wagner, Sweet, Butt, Lai & Cella 2009; Cheung et al., 2013; Joly et al., 2012; Cheung & Chang, 2013).

**Major Variables Defined**

Chemotherapy related cognitive impairment is defined as a multidimensional phenomenon that follows cancer chemotherapy treatment and involves a change in a person’s cognitive abilities. Domains that are affected include attention, executive functioning, information processing, motor speed, verbal ability, verbal memory, visual memory, and visuospatial ability (Kanaskie, 2012). Self-perceived cognitive change, cognitive change perceived by others, perceived cognitive abilities, and impact on quality of life will be the focus of this study.

High-dose melphalan is intravenously administered chemotherapy (100 to 200 mg/m2) given to patients with multiple myeloma in preparation for an autologous stem
cell transplant (Skinner et. al, 2004). Autologous stem cells removed from the patients are cryopreserved and are administered after high-dose chemotherapy.

Remission induction therapy refers to the initial chemotherapy treatment used to decrease the signs or symptoms of cancer or make them disappear prior to receiving high dose Melphalan and autologous stem cell transplant. Remission induction therapy for patients with myeloma can consist of one of two types of chemotherapy drugs: proteasome inhibitors or immunomodulatory drugs (IMiDs) or a combination of the two.

Theoretical Framework

Although a lack of agreement on the conceptual definition of cognitive impairment exists, theoretical integration of the concept has been suggested. Hess and Insel (2007) developed the Conceptual Model of Chemotherapy-related Changes in Cognitive Function. The assumption underlying the development of the conceptual model is that “to best develop effective strategies to prevent, care for, and minimize cognitive decline, healthcare professionals must have a clear understanding of the concept of chemotherapy-related change in cognitive function” (Hess & Insel, 2007 p. 982). This model suggests that two distinct pathways influence cognitive function change. One pathway involves the physiologic effects of cancer treatments and the other relates to the psychosocial impact of cancer diagnoses. This model proposes that the psychosocial impact of a cancer diagnosis leads to anxiety, stress, and depression.

Hess and Insel (2007) concluded that a variety of factors may contribute to changes in cognitive function because there are a multitude of physiologic and psychosocial changes that occur following a diagnosis of cancer. Their conclusion was
supported by the information obtained from their systematic review of cognitive impairment in the oncology setting. Knowing that changes may be related to more than just the exclusive impact of chemotherapy, Hess and Insel (2007) developed a model of cognitive decline experienced by these individuals. The conceptual model was developed with the aim that it would provide a structure for which future research may be based as well to provide a framework by which appropriate interventions can be utilized by clinicians to improve cognitive functioning, quality of life and overall well-being.

The Chemotherapy-Related Change in Cognitive Function conceptual model was developed using five themes: conceptual definitions, antecedents, moderators, mediators, and consequences. The data within each category were then synthesized to develop the conceptual model. The antecedents are preconditions of chemotherapy-related changes and are of two broad categories: psychological and social factors resulting from receiving the diagnosis of cancer and physiologic factors because of treatment (Hess & Insel, 2007).

The moderators are variables that can influence either the strength or direction of the relationship between an independent variable and a dependent variable such as chemotherapy and cognitive function, respectively. Examples of moderators include age, education, and general intelligence, age-related cognitive decline, disease states and other variables that are unrelated to cancer diagnoses. Mediators are divided into physiologic factors (e.g., type of chemotherapy, its dose and duration, use of concurrent medications, radiation therapy) and psychosocial factors (e.g., stress, depression, anxiety, and distress). Consequences are the outcomes of chemotherapy-related changes in cognitive function.
and are measurable. Examples of these include quality of life and functional ability (Hess & Insel, 2007).

Hess and Insel (2007) stated that the conceptual model needs to be further tested in research and refined prior to its use in the development and implementation of strategies to prevent or treat changes in cognitive function (see Figure 1).

![Figure 1: The Chemotherapy-Related Change in Cognitive Function conceptual model (Hess & Insel, 2007)](image)

**Summary**

The Conceptual Model of Chemotherapy-Related Changes in Cognitive Function provides an effective framework for this research. Research will further enhance the understanding of the concepts in this model and their relationships. Currently, one aspect of cognitive impairment that has yet to be determined is whether anxiety, depression, and
fatigue contributes to the incidence of the cognitive impairment experience, or whether the cognitive impairment experience is causal to anxiety, depression, and fatigue (Myers, 2009). For this reason and for the purpose of this research, the part of the conceptual model that will be applied towards this research will focus on the antecedents, the physiologic mediators on the self-reported and formally assessed changes in cognitive function and its effect on health-related quality of life.

Distress associated with impairment in cognitive function may have a significant effect on patient’s quality of life (Ahles & Saykin, 2001). Consequently, the need exists to learn about the incidence and causes of cognitive impairment in order to implement appropriate interventions towards managing this potential side effect. Currently, very few studies exist evaluating the effects of high dose chemotherapy. Additionally, no studies have evaluated the impact of high-dose melphalan followed by an autologous stem cell transplant on the cognitive function of patients with multiple myeloma.
Chapter Three: Methodology

Introduction

Cognitive impairment associated with chemotherapy has gained a significant amount of attention in research over the last two decades (Ferguson et. al, 2010). The advancement of chemotherapeutic treatments for cancer has allowed for long term survival in many cases. However, chemotherapeutic treatments are also accompanied by an array of unwanted side effects including cognitive impairment reported by cancer survivors. Chemotherapy related cognitive impairment is characterized by impairments in memory, attention, clarity of thought, executive functioning and speed of information processing. The impact of these cognitive changes in cognitive functioning on everyday life is reported to be considerable (Hodgson, Hutchinson, Wilson & Nettelbeck, 2012). Overall, this phenomenon seems to affect a considerable portion of individuals and for periods that may be well beyond treatment completion (Ferguson et. al, 2010).

Research Questions

1. What is the incidence of chemotherapy related cognitive impairment, “chemo brain”, in adult myeloma patients receiving high-dose melphalan followed by autologous stem cell transplant?

2. How effectively can the FACT-Cog longitudinally measure cognitive changes and perceived quality of life in patients with multiple myeloma who are receiving high dose chemotherapy?

Design
The proposed study is a longitudinal, multiple time series design with repeated measures. This research design will allow for obtaining patient self-reported cognitive functioning at four different time points (Appendix 2). Point A represents a baseline evaluation of cognitive status measured after diagnosis of multiple myeloma and prior to receiving any type chemotherapy treatment. The measures used at Point A will be recollected one-month post completion of remission induction therapy and/or prior to consolidation therapy with high dose melphalan (Point B). These measures will be repeated at Point C, which occurs one month post administration of high-dose Melphalan and stem-cell transplant. One final measurement will be obtained at Point D, six months post-transplant.

Sampling and Recruitment Procedures

The target population will be adult patients with multiple myeloma who will be receiving high-dose melphalan for an autologous stem cell transplant. A nonrandom convenience sample will be selected from patients being treated at one of three oncology clinics within a large health care organization in southern California. The treating physician specializing in hematology/oncology will share information about the study with eligible patients during a scheduled visit. If a patient expresses interest and gives permission, the referring provider will contact the principal investigator with the patient’s preferred means of initial contact. A meeting will be scheduled in a private quiet room in the patient’s own clinic and a consent form will be reviewed. Once adequately informed, the patient will be asked to sign a consent form that includes a release of clinical information from the patient record regarding clinical characteristics of their disease.
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process and subsequent treatment. Participants for this study will be recruited following the Health Insurance Portability and Accountability Act (HIPAA) guidelines.

Inclusion criteria for this study are adults at least 18 years of age with a diagnosis of multiple myeloma, able to read and understand English, and having ECOG performance status ratings of 0-3. Exclusion criteria include alcohol or drug addiction, having a comorbid condition that may affect cognitive status, such as traumatic brain injury, dementia, multiple sclerosis or psychosis. A sample size of 55 was calculated using G-Power, version 3.1.9.2 software (Faul, Erdfelder, Buchner & Lang, 2007). With an alpha level of 0.05, effect size of 0.20, and beta power of 0.95. A 20% increase to the calculated sample size was done to account for attrition resulting in a total sample size of 66 participants (see figure 2).
Data Collection

After requesting and obtaining approval from the Institutional Review Board (IRB), all patients who give informed consent (Appendix 1) will be scheduled to fill out the Fact-Cog questionnaire to measure self-perceived cognitive functioning. A self-report questionnaire will be used to collect information on the individual’s demographic characteristics of age, gender, ethnicity, level of education, date of diagnosis and ECOG performance status. Participants will fill out the self-report questionnaire at four different
time points. Point A represents a baseline evaluation of cognitive status measured after
diagnosis of multiple myeloma and prior to receiving any type chemotherapy treatment.

The measures used at Point A will be recollected one-month post completion of
remission induction therapy and/or prior to consolidation therapy with high dose
Melphalan (Point B). These measures will be repeated at Point C, which occurs one
month post administration of high-dose Melphalan and stem-cell transplant. One final
measurement will be obtained at Point D, six months post-transplant.

**Measurement Methods**

Demographic related variables will be obtained by a self-report questionnaire
including age, gender, ethnicity, highest level of education completed, date of diagnosis
of multiple myeloma and Eastern Cooperative Oncology Group (ECOG) performance
status. The Functional Assessment of Cancer Therapy – Cognitive Function version 3
(FACT-Cog) a self-reported measured of chemotherapy-related cognitive function will be
used in this study.

It is a 37 items self-report questionnaire with subscales consisting of the patients’
perceived cognitive impairments, perceived cognitive abilities, noticeability or comments
from others and impact of cognitive changes on quality of life. The original FACT-Cog
scale has been modified to form the basis for the FACT-Cog Version 2 and has been
refined leading to version 3 (Wagner, Sweet, Butt, Lai & Cella 2009). Internal
consistency using Cronbach’s Alpha for the FACT-Cog cognitive domain scores ranged
from 0.707 to 0.929 with satisfactory test-retest reliability (Cheung el. al, 2013).
**Coding and Scoring**

The FACT-Cog V3 will be scored as directed by the authors of the instrument. The scoring for two of the four subscales, perceived cognitive impairments and noticeability and comments from others, the scoring is 0 for “never,” 1 for “about once a week,” 2 for “two to three times a week,” 3 for “nearly every day” and 4 for “several times a day.” The scoring for the subscales, perceived cognitive abilities and impact on quality of life ranges from 0 to 4 for “not at all” to “very much,” respectively. Each test score will be converted into a standard z-score by using mean test scores and the standard deviations of the baseline measures as reference.

In addition to the patients’ safety, the patients’ privacy and confidentiality will be protected with the use of a locked file cabinet and database management system, all information is to be held in confidentiality in a locked file cabinet in the principle investigator’s office for a minimum of 7 years. Once the surveys are completed, the principal investigator will replace patient’s name with a code number, which means patient’s real name will not appear on the surveys thereafter. Additionally, no one will have access to this code number except for the PI.

**Data Management and Analysis**

Test results and questionnaires will be stored in a secure file cabinet as well as a secure database maintained by a database management system. The Statistical Package for Social Sciences (SPSS - version 22) will be used for data analyses. Appropriate steps will be used to test differences in the dependent measure across time. Confounding variables will also be analyzed to test their effect on the dependent variable. The F–test
repeated measures analysis of variance (ANOVA) for between and within group design will be used to analyze the data. Given that the assumptions of the repeated measures ANOVA is met, that is, the grouping variable has three or more categories, the variable measuring the characteristic of interest is normally distributed, the variable measuring the characteristic of interest is normally distributed with homogeneity of variance among all the groups, the repeated measures ANOVA will measure the differences in the mean questionnaire scores between the four different time points. The repeated measures ANOVA will also detect differences in dependent measures across time and determine variability and probable effect size. The data analysis will be done using ANOVA test, at an alpha level of 0.05. A post hoc analysis will be conducted to determine which of the means are different in order to draw a conclusion on the incidence of chemotherapy related cognitive impairment.

**Ethical Considerations**

IRB approval will be obtained prior to beginning the study. Ensuring the patients safety particularly in such a vulnerable population is crucial. All patients who give informed consent will be scheduled to complete the questionnaire at the individuals’ local clinic in a quiet private room. Ample amount of time will be provided for patients to complete the questionnaires. A general health and psychosocial assessment will be conducted prior to assessment to ensure patient has the functional ability and energy to complete the series of questions.

If a patient is feeling ill or other stressors present, the assessment can be rescheduled to accommodate the patient’s condition and a referral will be made to the
patient’s physician. Sufficient time will be provided to reduce the risk of respondent burden. In addition to the patients’ safety, the patients’ privacy and confidentiality will be protected with the use of a locked file cabinet and database management system, all information is to be held in confidentiality in a locked file cabinet in the principle investigator’s office for a minimum of 7 years. Once the surveys are completed, the principal investigator will replace patient’s name with a code number, which means patient’s real name will not appear on the surveys thereafter. Additionally, no one will have access to this code number except for the PI.

**Study Weaknesses**

There is a risk of bias in this study due to the convenience sampling technique. The participants in this study many not include members from all relevant segments of the population due to the method of non-probability sampling. A limitation is the likelihood of attrition as participants who initially enroll in the study may later not be eligible for high-dose Melphalan and transplant either due to inability to reach remission or other factors. Attrition may also be due to loss of participants through death.

Another limitation is the inability to control for the order of the treatment interventions. High-dose Melphalan cannot be tested exclusively without the presence of previously administered standard dose therapy. Consequently, variation in cognitive change may be attributable to or affected by standard dose chemotherapy. The two different classes of standard chemotherapy drugs may further influence the variation in cognitive change in different ways depending on the type of drug, protease inhibitors, IMiDs or a combination of both.
Other confounding variables include the possibility that the stem cell transplant may have an impact on cognitive change. Another point to consider is the possibility of the patient’s health condition or the presence of other situational stressors when being tested. Lastly, results of this study can only be generalized to those without any pre-existing neurological or psychiatric illness leaving out those that may be even more vulnerable to cognitive changes.
References


Appendix A

CONSENT TO PARTICIPATE IN RESEARCH

California State University, San Marcos

Jamila Faiq
Principal Investigator

Invitation to Participate

Jamila Faiq, a graduate student in nursing at California State University San Marcos, is conducting a study about the effects of high dose chemotherapy on cognitive functioning. You are invited to participate in this study because you have Multiple Myeloma and you are a stem cell transplant candidate.

Purpose

The purpose of the study is to learn about the effects of high dose chemotherapy on cognitive functioning and its effect on quality of life.

Description of Procedures

If you agree to participate, you will be asked to complete two questionnaires. One will ask you questions about yourself, such as your age and ethnicity in addition to your stage of treatment. The other questionnaire has 37 questions and is called the Fact-Cog survey. This self-report questionnaire is a tool to evaluate your cognitive function before, during, and after chemotherapy. It asks questions about your cognitive thinking, such as your memory and concentration as well as questions related to quality of life. You will be asked to fill out this questionnaire 4 times in the next few months. The first will be today, the second will be one month after completing your first course of chemotherapy. The third will be one month after receiving high-dose chemotherapy. The last questionnaire will be filled out 6 months after your stem cell transplant. You will fill out the Fact-Cog questionnaire at your regular scheduled appointment in a private and quiet room. This questionnaire will take about 30 – 45 minutes.
**Risks and Inconveniences**

There may be a risk that you feel uncomfortable, anxious or sad while answering the survey questions. There is also the potential risk for mental fatigue and frustration. There is also the loss of time to complete the survey. Remember, you can stop completing the surveys at any time you decide for any reason. Sufficient time will be provided to reduce the risk of any burden on you.

**Safeguards**

You have the right to refuse to answer any question that makes you uncomfortable. All information is to be held in confidentiality in a locked file cabinet in the principle investigator’s office for a minimum of 7 years. Once you complete the surveys, the principal investigator will replace your name with a code number, which means your real name will not appear on the surveys thereafter. Additionally, no one will have access to this code number except for the PI. You have the right to leave the study at any time without any consequence to you. Nothing about your medical care will change if you decide to stop being in the study. In addition to your safety, your privacy and confidentiality will be protected at all times. If you become upset and need assistance you will be immediately referred to your physician.

**Voluntary Participation**

Participation is voluntary. You may refuse to answer any question and/or quit at any time. Should you choose to quit, no one will be upset with you and your information will be destroyed right away. If you decide not to participate or quit, nothing will change about your healthcare treatment, your access to health care, or any other services to which you are entitled.

**Benefits**

While you will receive no direct benefit, the information learned may add to what is known about how chemotherapy affects patient’s thinking and memory. This may help health care providers take care of patients in the future.

**Incentives**

There will be no incentives offered for participating in this study.

**Questions**

If you have any questions about this study I will be happy to answer them now. If you have any questions in the future, please contact the principal investigators Jamila Faiq at (760) 214-7269 or faiq001@cougars.csusm.edu. If you have any questions about
your rights as a research participant, you may contact the CSUSM Institutional Review Board at (760) 750-4029.

I have read and understand this form, and consent to the research it describes to me. I have received a copy of this consent form for my records.

_________________________________________  ________________________
Signature of Participant                                      Date

_________________________________________
Name of Participant (Printed)

_________________________________________  ________________________
Signature of Principal Investigator                                      Date
Appendix B:

Timeline for Study

<table>
<thead>
<tr>
<th>Point</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point A</td>
<td>Represents a baseline evaluation of cognitive status measured after diagnosis of multiple myeloma and prior to receiving any type chemotherapy treatment.</td>
</tr>
<tr>
<td>Point B</td>
<td>Evaluation of cognitive status will be assessed one-month post completion of remission induction therapy and/or prior to consolidation therapy with high dose Melphalan.</td>
</tr>
<tr>
<td>Point C</td>
<td>Evaluation of cognitive status will be assessed one month post administration of high-dose Melphalan and stem-cell transplant</td>
</tr>
<tr>
<td>Point D</td>
<td>One final evaluation of cognitive status will be obtained at six months post-transplant.</td>
</tr>
</tbody>
</table>
Appendix C

FACT-Cognitive Function (Version 3)

Below is a list of statements that other people with your condition have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Never</th>
<th>About once a week</th>
<th>Two to three times a week</th>
<th>Nearly every day</th>
<th>Several times a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>CogA1 I have had trouble forming thoughts</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogA3 My thinking has been slow</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogC7 I have had trouble concentrating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogM9 I have had trouble finding my way to a familiar place</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogM10 I have had trouble remembering where I put things, like my keys or my wallet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogM12 I have had trouble remembering new information, like phone numbers or simple instructions</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogV13 I have had trouble recalling the name of an object while talking to someone</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogV15 I have had trouble finding the right word(s) to express myself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogV16 I have used the wrong word when I referred to an object</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogV17b I have had trouble saying what I mean in conversations with others</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
### Chemotherapy Related Cognitive Impairment in Multiple Myeloma

<table>
<thead>
<tr>
<th>CogF19</th>
<th>I have walked into a room and forgotten what I meant to get or do there... 0 1 2 3 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CogF23</td>
<td>I have had to work really hard to pay attention or I would make a mistake .... 0 1 2 3 4</td>
</tr>
<tr>
<td>CogF24</td>
<td>I have forgotten names of people soon after being introduced................ 0 1 2 3 4</td>
</tr>
</tbody>
</table>

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

<table>
<thead>
<tr>
<th>CogF25</th>
<th>My reactions in everyday situations have been slow ................ 0 1 2 3 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CogC31</td>
<td>I have had to work harder than usual to keep track of what I was 0 1 2 3 4</td>
</tr>
<tr>
<td>CogC32</td>
<td>My thinking has been slower than usual.............................. 0 1 2 3 4</td>
</tr>
<tr>
<td>CogC33a</td>
<td>I have had to work harder than usual to express myself clearly...... 0 1 2 3 4</td>
</tr>
<tr>
<td>CogC33c</td>
<td>I have had to use written lists more often than usual so I would not forget things ................. 0 1 2 3 4</td>
</tr>
<tr>
<td>CogMT1</td>
<td>I have trouble keeping track of what I am doing if I am interrupted .................................. 0 1 2 3 4</td>
</tr>
<tr>
<td>CogMT2</td>
<td>I have trouble shifting back and forth between different activities that require thinking .................. 0 1 2 3 4</td>
</tr>
</tbody>
</table>
Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>COMMENTS FROM OTHERS</th>
<th>Never</th>
<th>About once a week</th>
<th>Two to three times a week</th>
<th>Nearly every day</th>
<th>Several times a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>CogO1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogO2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogO3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogO4</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>PERCEIVED COGNITIVE ABILITIES</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>CogPC1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogPV1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogPM1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogPM2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogPF1</td>
<td>I am able to pay attention and keep track of what I am doing without extra effort</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>CogPCH 1</td>
<td>My mind is as sharp as it has always been</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>CogPCH 2</td>
<td>My memory is as good as it has always been</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>CogPMT 1</td>
<td>I am able to shift back and forth between two activities that require</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>CogPMT 2</td>
<td>I am able to keep track of what I am doing, even if I am interrupted</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

### IMPACT ON QUALITY OF LIFE

<table>
<thead>
<tr>
<th>CogQ35</th>
<th>I have been upset about these problems</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogQ37</td>
<td>These problems have interfered with my ability to work</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogQ38</td>
<td>These problems have interfered with my ability to do things I enjoy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>CogQ41</td>
<td>These problems have interfered with the quality of my life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Appendix D:

IRB Application

California State University
SAN MARCOS

Application for Approval for Research Involving Human Subjects:
Full or Expedited Review

Submission Procedures:
1. The researcher completes application
2. If the researcher is a student, their faculty advisor reviews application and completes signature field (last page) then returns the signed document to the student. Instructions for signing this document.
3. The researcher submits the application and accompanying documents at http://csusirb.submittable.com

For assistance completing this form, please review the resources located at www.csusm.edu/irb
If you have any questions, please refer to the IRB website or contact the IRB staff at (760) 750-4629 or irb@csusm.edu.

Please answer each section completely and as succinctly as possible. Use lay terms as IRB members have diverse backgrounds.

<table>
<thead>
<tr>
<th>Full Review</th>
<th>Expedited Review</th>
<th>Proposed Start Date</th>
<th>06/05/2015</th>
</tr>
</thead>
</table>

Project Title: Chemotherapy Related Cognitive Impairment

Faculty/Staff Investigator:

Name: WENDY HANSBROUGH PHD, RN
Phone Number: (760) 750-7550
E-mail: whansbro@csusm.edu
Date CITI Completed

Student Investigator: (If the student is the primary investigator)

Name: Jamila Faiq
Phone Number: (760) 234-7269
E-mail: jmsfaiq@gmail.com
Date Training Completed: 06/28/2015

Faculty Advisor Name: WENDY HANSBROUGH
Phone Number: (760) 750-7550
E-mail: whansbro@csusm.edu
Date CITI Completed

Date CITI Completed

Date CITI Completed
1. Purpose of Project and Project Background

Describe your research question, including why the question is important, and how your study will attempt to answer it. Include how your literature review supports this with at least three citations. (Do not exceed one page—Use lay language.)

Little is known about cognitive impairment related to chemotherapy. Patients who receive chemotherapeutic drugs report cognitive impairment during or subsequent to treatment (Raffa, 2010). It is vital to determine the long-term consequences of cognitive change related to chemotherapy and its impact on quality of life. A great need exists for research focused on the effects of high dose chemotherapy on cognitive function. In addition, large-scale prospective clinical trials with longitudinal design and appropriate controls to evaluate the probability of chemotherapy related cognitive impairment is needed. Currently, there have been no studies that have investigated the effects of high dose Melphalan on cognitive function for individuals with multiple myeloma in the setting of a stem cell transplant.

The research question is “What is the incidence of chemotherapy related cognitive impairment, “chemo brain”, in adult myeloma patients receiving high-dose Melphalan followed by autologous stem cell transplant?”

2. Recruitment Procedures & Participant Population

A) List the expected number of participants for each population group included in this study. 66 adult patients with multiple myeloma who will be receiving high-dose Melphalan for an autologous stem cell transplant.

B) Describe all characteristics relevant to being selection of participants. (e.g., demographics, ethnicity, vulnerabilities, etc.) Explain why you are targeting this specific population.

The target population will be adult patients with multiple myeloma who will be receiving high-dose Melphalan for an autologous stem cell transplant. A nonrandom convenience sample will be selected from patients being treated at one of three oncology clinics within a large health care organization in southern California.

Inclusion criteria for this study are adults at least 18 years of age with a diagnosis of multiple myeloma, able to read and understand English, and having ECOG performance status ratings of 0-3. A sample size of 55 was calculated using G*Power, version 3.1.9.2 software with an alpha level of 0.05, effect size of 0.20, and beta power of 0.95. A 20% increase to the calculated sample size was done to account for any loss factors resulting in a total sample size of 66 participants.
Q) Indicate whether anyone might be excluded from participating and explain why.
Exclusion criteria include alcohol or drug addiction, having a comorbid condition that may affect cognitive status, such as traumatic brain injury, dementia, multiple sclerosis or psychosis.

D) How will you find, recruit, or identify potential subjects? How will you select, from the volunteers, the final group of participants? Submit flyers, posters, or other oral or written invitations used to recruit potential participants.
A nonrandom convenience sample will be selected from patients being treated at one of three oncology clinics within a large health care organization in southern California.

E) Will you be offering an incentive?
☐ Yes  ☐ No
If yes, please explain procedure for any incentives that will be offered. Include how much participants must do to be eligible to receive credit.

   Explain for each population participating in your research.
   See the IRB web page on Informed Consent. See also Language Requirements.

At How and when will you explain the study and the required elements of Informed Consent? Will you be doing this or will it be handled by a research assistant?
The student investigator will explain the study and the required elements of the Informed Consent to every participating patient.
B) How much time will participants have to consider participating between the explanation described above, the receipt of the consent document, and the beginning of study?

2 weeks

C) If there are subjects under the age of 18, how will the study be explained to them? How will parental consent and child assent be handled?

N/A

D) If you are requesting a Waiver of Consent or a Waiver of Documentation of Consent, explain why this waiver is needed. Outline alternative procedures for obtaining consent or providing study information (e.g., information sheet, introduction screen for web survey, etc.).

N/A

E) Indicate the primary language(s) of your participants. If any participants’ is not fluent and comfortable with English, explain how you will ensure that participants’ understanding of the activity for which they are giving consent.

English

4. Procedures and Methodology

Provide descriptions of each distinct procedure and each population group.

A) Provide a step-by-step explanation of your research activities and methodologies that involve human subjects. Be thorough.

**Time-line for Study**

Point A Represents a baseline evaluation of cognitive status will be measured after diagnosis of multiple myeloma and prior to receiving any type chemotherapy treatment.

Point B Evaluation of cognitive status will be assessed one month post completion of remission induction therapy and/or prior to consolidation therapy with high dose Melphalan.

Point C Evaluation of cognitive status will be assessed one month post administration of high-dose Melphalan and stem-cell transplant

Point D One final evaluation of cognitive status will be obtained at six months post-transplant.
B) Where will the research be conducted? Describe any risks or confidentiality issues related to using this location.

At one of three oncology clinics within a large health care organization in southern California.

☐ State the specific dates/timeframe in which you plan to conduct your research.

The study will be over a 24 months period. Data collection will start on 01/01/2016 and will end by 01/01/2017.

5. Participant Debriefing or Feedback.

If deception is involved in your research, participants should be debriefed about the nature of the study as soon as possible. Participants should be given the opportunity to request a copy of the results of the study or our final report.

A) Describe any feedback or information you will offer participants.

Participants will have the opportunity to request a copy of the results of the study and the final report.

6. Risks

List risks for each population participating in the research and for each methodology. Please be sure the risks listed here match the risks mentioned in your consent letter or information sheets. Consider all risks very carefully. For more information on risks, see Examples of Risk.

A) Explain potential risks to your participants. Risks may be physical, psychological (e.g., strong emotional reactions to research questions), or inconveniences (e.g., time required).

There may be a risk that you feel uncomfortable, anxious or sad while answering the survey questions. There is also the potential risk for mental fatigue and frustration. There is also the loss of time to complete the survey.

B) Vulnerable Subjects: Select which, if any, of the following vulnerable subjects will be involved in your research.

☐ Pregnant women, human fetuses, neonates (see Federal Guidelines, 45CFR26, subpart B)
☐ Prisoners (see Federal Guidelines, 45CFR26, subpart C)
☐ Children (see Federal Guidelines, 45CFR26, subpart D)
☐ Other Vulnerable Populations such as persons with cognitive disabilities, economically or educationally disadvantaged persons, etc.

☐ Describe any special risks to vulnerable populations or your population profile

N/A
D) List risks related to confidentiality of data. What could happen if an unauthorized person accessed the data? For instance, participant's identify or personal information could be known by others.

In addition to the patients' safety, the patients' privacy and confidentiality will be protected with the use of a locked file cabinet and database management system.

E) Will any personal identifying data be recorded? If so, what information will be recorded?
(e.g., Social security number, drivers license number, student id, address, phone number, birth date, personal email address)

Patients names and date of birth.

7. Safeguard Procedures to Minimize Risks.

A) Please respond to each risk that you listed in #6 above. State how you will minimize each risk and protect confidentiality.

All patients who give informed consent will be scheduled to complete the questionnaire at the individuals' local clinic in a quiet private room. Ample amount of time will be provided for patients to complete the questionnaires. A general health and psychosocial assessment will be conducted prior to assessment to ensure patient has the functional ability and energy to complete the series of questions.

If a patient is feeling ill or other stressors present, the assessment can be rescheduled to accommodate the patient's condition. Sufficient time will be provided to reduce the risk of respondent burden. In addition to the patients' safety, the patients' privacy and confidentiality will be protected with the use of a locked file cabinet and database management system, all information is to be held in confidentiality in a locked file cabinet in the principle investigator's office for a minimum of 7 years. Once the surveys are completed, the principal investigator will replace patient's name with a code number, which means patient's real name will not appear on the surveys thereafter. Additionally, no one will have access to this code number except for the PI.

B) How will you safeguard data? Where/how will data be stored? Who will have access to the data? How will access be limited?

The patients' privacy and confidentiality will be protected with the use of a locked file cabinet and database management system. The primary investigator will be the only one with access to data.

C) List referrals and/or resources that may be offered if a participant has a strong emotional response or a physical injury (e.g., clinics or shelters, medical or psychological referrals).

N/A
### 8. Study Benefits

A) Discuss any potential individual and/or societal benefits. Note, often there is no direct benefit for the participants. However, the study may contribute to the literature and/or future research.

There is no direct benefit for the participants. The information will be used to investigate the incidence of cognitive impairment related to high dose chemotherapy and assess the impact of cognitive changes on quality of life.

B) Do the benefits from this study exceed the risks to participants? Please explain.

N/A

### 9. Researcher(s) qualifications and experience.

A) Briefly outline the primary researcher(s)'s qualifications and experiences relative to the subject of this research.

The student investigator is an RN with 5 years of oncology experience in a bone marrow transplant unit.

B) If this is a student project, include faculty sponsor's qualifications.

Wendy Hansbrough, PhD, RN  
Assistant Professor & Med/Surg Lead

C) If using student or research assistants, please state how you will ensure that these assistants are trained and qualified to assist. All assistants should complete the CITI training on the protection of human participants in research.

N/A
Time to Review:

Expedited reviews are reviewed by one committee member with an average approval time of approximately three weeks. Questions from reviewers and approval paperwork will be sent to the email address provided on the application at the time of submission.

Full reviews are reviewed by the full committee at an IRB meeting. Approvals on full reviews may take 4-6 weeks. Questions from the committee and approval paperwork will be sent to the email address provided on the application at the time of submission. All “full review” applications are copied to Risk Management.

Electronic Submission:

1. Once the student has completed the application they should e-mail this application to their faculty advisor for review.
2. The faculty should sign in the signature field below and then return the application to the student. Instructions on how to sign this document can be found here.
3. The student will then submit through the online submission system at: http://cuamirb.submittable.com

Faculty Signature

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Appendix E:

Grant Application

2016 ONS Foundation Research Grant Program

LETTER OF INTENT FORM

Please review Letter of Intent instructions for specific requirements.

Letters of Intent are to be emailed to research@onsfoundation.org by August 15, 2015.

Note: Applications without a prior letter of intent form will not be considered for funding. No letters will be accepted after 8/15.

Principal Investigator: (Name, credentials, institutional affiliation and previous RESEARCH funding experience and amount of funding)

Name & Credentials: Jamila Faiq RN BSN

Institution: California State University San Marcos

Email Address: faiq001@cougars.csusm.edu

Previous Research Funding Experience, including funding amount: n/a

Title of the project:
Chemotherapy Related Cognitive Impairment

Brief statement describing the proposed study, including the following areas:
(Please limit the description to 30 lines)

Purpose/Background: Chemotherapeutic drugs have contributed to substantial improvements in the survival of cancer patients. However, such drugs have adverse effects that can be debilitating and even life-threatening. One adverse effect is “chemo brain;” a very poorly understood but a well-documented phenomenon. Chemo...
brain refers to the cognitive deficits that are experienced by some individuals during and following chemotherapy (Staat & Segator, 2005). Although "chemo brain", formally termed "Chemotherapy-Related Cognitive Impairment", has been documented as early as 1980 by psychiatrists, it has only recently been addressed consistently in the literature (Kanaskie, 2012; Myers, 2008). Presently, there is not a standard measurement or assessment of cognitive function in individuals with cancer nor are there established treatments available for patients who present with cognitive complaints (Hess & Insel, 2007). Some studies have demonstrated a lack of correlation between patient self-report of cognitive dysfunction and consequent performance on neurocognitive tests (Wefel et al., 2004; Evens & Eschiti, 2009). Some patients who receive cancer chemotherapeutic drugs report cognitive impairment during or subsequent to treatment while others do not and standardized tests detect these deficits in cognitive ability of some cancer survivors but not all (Raffa, 2010). It is not known why certain patients experience cognitive deficits or why it persists in some and resolves in others. Understanding the state of the science is imperative in determining the long-term consequences of cognitive change and its impact on quality of life.

A great need exists for research focused on the effects of high dose chemotherapy on cognitive function. In addition, large-scale prospective clinical trials with longitudinal design and appropriate controls to evaluate the probability of chemotherapy related cognitive impairment are needed. Currently, there are no reported studies that have investigated the effects of high dose Melphalan on cognitive function for individuals with multiple myeloma in the setting of a stem cell transplant. The concept of impaired cognitive function related to cancer treatment is important to nursing as it pertains to understanding the experience of the phenomenon and the exploration of strategies to manage the change (Kanaskie, 2012). Problems related to cognitive function may be subtle and may not be objectively evident, thus making assessment difficult. Patients presenting with cognitive complaints need to be assessed to determine appropriate intervention. Symptoms associated with cognitive dysfunction can negatively affect one’s quality of life by interfering with daily routines and planning abilities (Hafner, 2009).
When the impact of cognitive impairment related to chemotherapy is better understood, appropriate interventions can be developed to manage these changes and help individuals cope with cognitive changes.

**Aims:** The aims of this study are to measure the incidence of cognitive impairment in adult myeloma patients receiving high-dose melphalan followed by autologous stem cell transplant in addition to investigate how these patients perceive their cognitive abilities over time. Additionally, this study seeks to determine the effectiveness of the FACT-Cog, a self-report measuring tool in measuring cognitive changes overtime.

**Research Team:** (names, credentials, institutional affiliations, role on the team, previous completed RESEARCH funding experience AND amount of funding)

*Note: At least one team member must have received and completed RESEARCH funding greater than $100,000.*

n/a

**List of potential research sites, if applicable:**
Three oncology clinics in Southern California
Purpose

Chemotherapeutic drugs have contributed to substantial improvements in the survival of cancer patients. However, such drugs have adverse effects that can be debilitating. One adverse effect is “chemo brain;” a very poorly understood but a well-documented phenomenon. Chemo brain refers to the cognitive deficits that are experienced by some individuals during and following chemotherapy (Staat & Segator, 2005). Presently, there is not a standard measurement or assessment of cognitive function in individuals with cancer nor are there established treatments available for patients who present with cognitive complaints (Hess & Insel, 2007). Some patients who receive cancer chemotherapeutic drugs report cognitive impairment during or subsequent to treatment while others do not and standardized tests detect these deficits in cognitive ability of some cancer survivors but not all (Raffa, 2010). It is not known why certain patients experience cognitive deficits or why it persists in some and resolves in others.

Significance/Implications for Practice

The concept of impaired cognitive function related to cancer treatment is important to nursing as it pertains to understanding the experience of the phenomenon and the exploration of strategies to manage the change (Kanaskie, 2012). Understanding the state of the science is imperative in determining the long-term consequences of cognitive change and its impact on quality of life. Patients presenting with cognitive complaints
need to be assessed to determine appropriate intervention. When the impact of cognitive impairment related to chemotherapy is better understood, appropriate interventions can be developed to manage these cognitive changes and help individuals cope.

**Specific Aims/Main Research Variables**

A great need exists for research focused on the effects of high dose chemotherapy on cognitive function. In addition, large-scale prospective clinical trials with longitudinal design and appropriate controls to evaluate the probability of chemotherapy related cognitive impairment are needed. This study aims to measure the incidence of cognitive impairment in adult myeloma patients receiving high-dose melphalan followed by autologous stem cell transplant in addition to investigate how these patients perceive their cognitive abilities over time. Additionally, this study seeks to determine the effectiveness of the FACT-Cog, a self-report measuring tool in measuring cognitive changes overtime.

**Conceptual Model**

This study will be guided by the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function, which incorporates a variety of pathways and factors that may contribute to changes in cognitive function.

**Design/Methods**

A longitudinal, multiple time series design with repeated measures will be utilized. This research design will allow for obtaining patient self-reported cognitive functioning using the FACT-Cog questionnaire at four different time points including an initial baseline evaluation of cognitive status measured after diagnosis of multiple myeloma. Subsequent measurements will be taken after completion of remission induction therapy, after
administration of high-dose Melphalan and a final measurement six months post-transplant.

Setting/Sample

The target population will be adult patients with multiple myeloma who will be receiving high-dose melphalan for an autologous stem cell transplant. A nonrandom convenience sample will be selected from patients being treated at one of three oncology clinics within a large health care organization in southern California. The measurements will be conducted during the participant’s scheduled visit in a private quite room.

Project Narrative Approach

Introduction

Cognitive impairment associated with chemotherapy has gained a significant amount of attention in research over the last two decades (Ferguson et. al, 2010). The advancement of chemotherapeutic treatments for cancer has allowed for long term survival in many cases. However, chemotherapeutic treatments are also accompanied by an array of unwanted side effects including cognitive impairment reported by cancer survivors. Chemotherapy related cognitive impairment is characterized by impairments in memory, attention, clarity of thought, executive functioning and speed of information processing. The impact of these cognitive changes in cognitive functioning on everyday life is reported to be considerable (Hodgson, Hutchinson, Wilson & Nettelbeck, 2012). Overall, this phenomenon seems to affect a considerable portion of individuals and for periods that may be well beyond treatment completion (Ferguson et. al, 2010).
Purpose

1. What is the incidence of chemotherapy related cognitive impairment, “chemo brain”, in adult myeloma patients receiving high-dose melphalan followed by autologous stem cell transplant?
2. How effectively can the FACT-Cog longitudinally measure cognitive changes and perceived quality of life in patients with multiple myeloma who are receiving high dose chemotherapy?”

Significance

The subject of cognitive problems following chemotherapy have been gaining interest in research and are continuing to be studied in order to gain a better understanding of the phenomenon. When the impact of cognitive impairment related to chemotherapy is better understood, appropriate interventions can be developed to manage these changes and help individuals cope with cognitive changes. Chemotherapy related cognitive impairment is typically not discussed prior to the initiation of cancer treatment and many nurses are not prepared to educate patients regarding this potential side effect (Myers & Teel, 2008).

The concept of impaired cognitive function related to cancer treatment is important to nursing as it pertains to understanding the experience of the phenomenon and the exploration of strategies to manage the change (Kanaskie, 2012). Problems related to cognitive function may be subtle and may not be objectively evident, thus making assessment difficult. Patients presenting with cognitive complaints need to be assessed to determine appropriate intervention. Symptoms associated with cognitive
dysfunction can negatively affect one’s quality of life by interfering with daily routines and planning abilities (Hafner, 2009).

Another concern regarding chemotherapy-induced cognitive impairment relevant to nursing practice is that this potential side effect is generally not discussed as a potential adverse side effect with patients prior to the initiation of treatment. Many nurses are not prepared to educate patients and families regarding the potential development of cognitive impairment (Myers & Teel, 2008). Consequently, many patients are unaware of it and the impact it may have on their cognitive functioning (Evens & Eschiti, 2009).

Understanding the cognitive changes that may occur as a result of chemotherapy is imperative for care providers in order to manage, improve, or maintain functional ability in addition to supporting health-related quality of life.

**Framework**

Although a lack of agreement on the conceptual definition of cognitive impairment exists, theoretical integration of the concept has been suggested. Hess and Insel (2007) developed the Conceptual Model of Chemotherapy-related Changes in Cognitive Function. The assumption underlying the development of the conceptual model is that “to best develop effective strategies to prevent, care for, and minimize cognitive decline, healthcare professionals must have a clear understanding of the concept of chemotherapy-related change in cognitive function” (Hess & Insel, 2007 p. 982). This model suggests that two distinct pathways influence cognitive function change. One pathway involves the physiologic effects of cancer treatments and the other relates to the psychosocial impact of cancer diagnoses.
Hess and Insel (2007) concluded that a variety of factors may contribute to changes in cognitive function because there are a multitude of physiologic and psychosocial changes that occur following a diagnosis of cancer. The conceptual model was developed with the aim that it would provide a structure for which future research may be based as well to provide a framework by which appropriate interventions can be utilized by clinicians to improve cognitive functioning, quality of life and overall well-being. The Chemotherapy-Related Change in Cognitive Function conceptual model was developed using five themes: conceptual definitions, antecedents, moderators, mediators, and consequences. The data within each category were then synthesized to develop the conceptual model. The antecedents are preconditions of chemotherapy-related changes and are of two broad categories: psychological and social factors resulting from receiving the diagnosis of cancer and physiologic factors because of treatment (Hess & Insel, 2007).

The moderators are variables that can influence either the strength or direction of the relationship between an independent variable and a dependent variable such as chemotherapy and cognitive function, respectively. Examples of moderators include age, education, and general intelligence, age-related cognitive decline, disease states and other variables that are unrelated to cancer diagnoses. Mediators are divided into physiologic factors (e.g., type of chemotherapy, its dose and duration, use of concurrent medications, radiation therapy) and psychosocial factors (e.g., stress, depression, anxiety, and distress). Consequences are the outcomes of chemotherapy-related changes in cognitive function.
and are measurable. Examples of these include quality of life and functional ability (Hess & Insel, 2007).

The Conceptual Model of Chemotherapy-Related Changes in Cognitive Function provides an effective framework for this research. Research will further enhance the understanding of the concepts in this model and their relationships. Currently, one aspect of cognitive impairment that has yet to be determined is whether anxiety, depression, and fatigue contributes to the incidence of the cognitive impairment experience, or whether the cognitive impairment experience is causal to anxiety, depression, and fatigue (Myers, 2009). For this reason and for the purpose of this research, the part of the conceptual model that will be applied towards this research will focus on the antecedents, the physiologic mediators on the self-reported and formally assessed changes in cognitive function and its effect on health-related quality of life.

**Review of Literature**

Little or no change in cognitive ability on standard cognitive assessment instruments have been found despite self-reports of perceived cognitive changes by the study participants (Kanaskie, 2012). There is also an ongoing debate regarding which method of measurement is the gold standard for assessment of cognitive change related to chemotherapy; subjective self-report, objective neuropsychological evaluation or neuroimaging. Unfortunately, methodological difficulties in study designs have resulted not only in underestimating the magnitude of the problem, but even its existence (Raffa, 2009).
Recent studies have incorporated neuroimaging tests as a useful tool in identifying areas of the brain affected by chemotherapy and seek to provide a rationale for patient self-reports of cognitive impairment despite normal performance on the neurocognitive tests (Myers, 2008). Raffa (2009) has supported the use of neuroimaging techniques to address the inconsistency in the methods used to measure cognitive deficits. Neuropsychological testing in a twin study demonstrated similar results; however, the twin who underwent chemotherapy for breast cancer reported problems with cognitive function and had markedly differing structural and functional MRI images. This suggests that physiologic mechanisms may be present in those who experience cognitive dysfunction post-chemotherapy, in the absence of impaired neuropsychological performance (Wagner et. al, 2009).

Very few studies have examined the relationship between chemotherapy and cognitive impairment in cancer patients other than those diagnosed with breast cancer. One study conducted by Potrata, Cavet, Howe, Blair and Molassiotis, (2010) explored cognitive impairments in patients with multiple myeloma in order to gain an understanding of cognitive impairments and concerns as described by the patients. This phenomenological qualitative study included 4 informants who were less than one year from diagnosis, two who were between 1-5 years from diagnosis and nine who were more than 5 years after their initial diagnosis. Eleven of the patients who accounted for 73.3% of the sample had received a stem cell transplant. Subjective cognitive impairments such as poor recall, problems with short-term memory and lack of concentration were self-reported by 10 patients (66%). It was found that one
of the frequent coping strategies patients employed to address the problem of poor short-term memory and concentration was denial. Overall, the research indicates that a considerable number of myeloma patients may suffer from bothersome cognitive difficulties affecting their personal and professional lives and that these changes can be permanent for some. The most severe problems with cognitive functions included those patients who have undergone stem cell transplants alluding to the importance of research on the potential effects of stem cell transplantation.

Another study assessed for cognitive impairments in patients with lung cancer. Whitney et al (2008) reported the results of a pilot study which examined 14 stage III non-small cell lung cancer patients who received treatment with cisplatin, etoposide, and radiotherapy. Patients were evaluated with a comprehensive battery of examiner-administered cognitive tests and self-reported questionnaires before receiving chemotherapy and at one and seven months after treatment. The baseline assessment showed that 71% of patients (n=10) were judged to be cognitively impaired using the Hopkins Verbal Learning Test, a measuring verbal learning and memory (recognition and recall). This study looked at different variables that may impact the cognitive test scores such as laboratory values of TSH, homocysteine, or hemoglobin and found no statistically significant correlations.

One month post chemotherapy tests demonstrated a decline in cognitive function in 62% of the patients (n=8) with the most significant changes seen in the measure of conceptual flexibility but were also noted on all five other neuropsychological measures utilized in the study. Of the eight patients, two passed away and one dropped out leaving
five patients to compare the 7-month evaluation to the initial one-month follow up. Although the sample size was small, the results indicated that cognitive declines were temporary. This study also found no statistically significant correlations between neuropsychological test results and mood ratings, fatigue ratings, quality of life variables, or age at any of the three assessment time points.

Cognitive complaints and impairment were also evaluated in patients with testicular cancer following bleomycin, etoposide, and cisplatin (BEP) chemotherapy. Schagen et al (2007) compared three groups of patients with testicular cancer: those who received chemotherapy after surgery, received radiotherapy after surgery, or received surgery only. The neuropsychological status of all patients was assessed using a standard battery of neuropsychological tests in addition to interviewing patients regarding cognitive problems, health-related quality of life, anxiety and depression, and fatigue.

Of the 182 patients included in the study, 70 received chemotherapy after surgery, 57 were treated with radiotherapy after surgery, and 55 received surgery only. Self-reported cognitive problems were equal between the surgery plus chemotherapy group and surgery plus radiotherapy group (32%) and 27% in the surgery only group. When assessing for the health-related quality of life, anxiety, depression and fatigue, no significant differences were found between the three groups except for the global quality of life scale in which the surgery plus radiotherapy group reported lower scores indicating a lower level of functioning. The study found that, the percentage of patients classified as neuropsychologically impaired in the surgery plus chemotherapy group remained significantly different from the surgery only group (p= 0.038) and from the
surgery plus radiotherapy group (p=0.070). Furthermore, this study found no significant correlation between the overall cognitive impairment score and the occurrence of cognitive problems reported at the interview. This study suggests that the self-reported cognitive problems were related to the anxiety and depression scales of the Hopkins Symptom Checklist. The time since treatment was not found to influence the relationship between the self-reported problems, or the relationship between self-reported problems and neuropsychological test results.

In many studies, neuropsychological tests used to evaluate cognitive problems objectively, did not appear to be sensitive enough to detect subtle changes related to chemotherapy treatments (Joly et al., 2012). Consequently, the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) scale (Appendix 3) was developed to address this void. Items on the scale were identified through qualitative analysis of interviews with expert oncologists and patients following chemotherapy. The scale demonstrated a high level of internal consistency reliability using Cronbach’s coefficient alpha (0.707–0.929) when pretested with cancer patients undergoing chemotherapy treatment (Wagner, Sweet, Butt, Lai & Cella 2009; Cheung et al., 2013; Joly et al., 2012; Cheung & Chang, 2013).

**Design**

The proposed study is a longitudinal, multiple time series design with repeated measures. This research design will allow for obtaining patient self-reported cognitive functioning at four different time points. Point A represents a baseline evaluation of cognitive status measured after diagnosis of multiple myeloma and prior to receiving any
type chemotherapy treatment. The second self-report questionnaire will be collected one-month post completion of remission induction therapy and/or prior to consolidation therapy with high dose melphalan (Point B). These measures will be repeated at Point C, which occurs one month post administration of high-dose Melphalan and stem-cell transplant. One final measurement will be obtained at Point D, six months post-transplant.

**Sample and Settings**

The target population will be adult patients with multiple myeloma who will be receiving high-dose melphalan for an autologous stem cell transplant. A nonrandom convenience sample will be selected from patients being treated at one of three oncology clinics within a large health care organization in southern California. The treating physician specializing in hematology/oncology will share information about the study with eligible patients during a scheduled visit. If a patient expresses interest and gives permission, the referring provider will contact the principal investigator with the patient’s preferred means of initial contact. A meeting will be scheduled in a private quiet room in the patient’s own clinic and a consent form will be reviewed. Once adequately informed, the patient will be asked to sign a consent form that includes a release of clinical information from the patient record regarding clinical characteristics of their disease process and subsequent treatment. Participants for this study will be recruited following the Health Insurance Portability and Accountability Act (HIPAA) guidelines.
Inclusion criteria for this study are adults at least 18 years of age with a diagnosis of multiple myeloma, able to read and understand English, and having ECOG performance status ratings of 0-3. Exclusion criteria include alcohol or drug addiction, having a comorbid condition that may affect cognitive status, such as traumatic brain injury, dementia, multiple sclerosis or psychosis. A sample size of 55 was calculated using G-Power, version 3.1.9.2 software (Faul, Erdfelder, Buchner & Lang, 2007). With an alpha level of 0.05, effect size of 0.20, and beta power of 0.95. A 20% increase to the calculated sample size was done to account for attrition resulting in a total sample size of 66 participants.

**Experimental variables**

Chemotherapy related cognitive impairment is defined as a multidimensional phenomenon that follows cancer chemotherapy treatment and involves a change in a person’s cognitive abilities. Domains that are affected include attention, executive functioning, information processing, motor speed, verbal ability, verbal memory, visual memory, and visuospatial ability (Kanaskie, 2012). Self-perceived cognitive change, cognitive change perceived by others, perceived cognitive abilities, and impact on quality of life will be the focus of this study.

High-dose melphalan is intravenously administered chemotherapy (100 to 200 mg/m2) given to patients with multiple myeloma in preparation for an autologous stem cell transplant (Skinner et. al, 2004). Autologous stem cells removed from the patients are cryopreserved and are administered after high-dose chemotherapy.
Remission induction therapy refers to the initial chemotherapy treatment used to decrease the signs or symptoms of cancer or make them disappear prior to receiving high dose Melphalan and autologous stem cell transplant. Remission induction therapy for patients with myeloma can consist of one of two types of chemotherapy drugs: proteasome inhibitors or immunomodulatory drugs (IMiDs) or a combination of the two.

The dependent variable in this study is cognitive function as measured by the self-reported FACT-Cog (Version 3). The main independent variable in this study is high-dose Melphalan (100-200mg/m2). Additionally, time is also a variable that may influence cognitive functions as well.

**Instruments and Measurement Methods**

Demographic related variables will be obtained by a self-report questionnaire including age, gender, ethnicity, highest level of education completed, date of diagnosis of multiple myeloma and Easter Cooperative Oncology Group (ECOG) performance status. The Functional Assessment of Cancer Therapy – Cognitive Function version 3 (FACT-Cog) a self-reported measured of chemotherapy-related cognitive function will be used in this study.

It is a 37 items self-report questionnaire with subscales consisting of the patients’ perceived cognitive impairments, perceived cognitive abilities, noticeability or comments from others and impact of cognitive changes on quality of life. The original FACT-Cog scale has been modified to form the basis for the FACT-Cog Version 2 and has been refined leading to version 3 (Wagner, Sweet, Butt, Lai & Cella 2009). Internal
consistency using Cronbach’s Alpha for the FACT-Cog cognitive domain scores ranged from 0.707 to 0.929 with satisfactory test-retest reliability (Cheung et al. 2013).

**Data Collection**

After requesting and obtaining approval from the Institutional Review Board (IRB), all patients who give informed consent (Appendix 1) will be scheduled to fill out the Fact-Cog questionnaire to measure self-perceived cognitive functioning. A self-report questionnaire will be used to collect information on the individual’s demographic characteristics of age, gender, ethnicity, level of education, date of diagnosis and ECOG performance status. Participants will fill out the self-report questionnaire at four different time points. Point A represents a baseline evaluation of cognitive status measured after diagnosis of multiple myeloma and prior to receiving any type chemotherapy treatment.

The measures used at Point A will be recollected one-month post completion of remission induction therapy and/or prior to consolidation therapy with high dose Melphalan (Point B). These measures will be repeated at Point C, which occurs one month post administration of high-dose Melphalan and stem-cell transplant. One final measurement will be obtained at Point D, six months post-transplant.

**Data Analysis and Interpretation**

The FACT-Cog V3 will be scored as directed by the authors of the instrument. The scoring for two of the four subscales, perceived cognitive impairments and noticeability and comments from others, the scoring is 0 for “never,” 1 for “about once a week,” 2 for “two to three times a week,” 3 for “nearly every day” and 4 for “several times a day.” The scoring for the subscales, perceived cognitive abilities and impact on
quality of life ranges from 0 to 4 for “not at all” to “very much,” respectively. Each test score will be converted into a standard \( z \)-score by using mean test scores and the standard deviations of the baseline measures as reference.

Test results and questionnaires will be stored in a secure file cabinet as well as a secure database maintained by a database management system. The Statistical Package for Social Sciences (SPSS - version 22) will be used for data analyses. Appropriate steps will be used to test differences in the dependent measure across time. Confounding variables will also be analyzed to test their effect on the dependent variable. The F–test repeated measures analysis of variance (ANOVA) for between and within group design will be used to analyze the data. Given that the assumptions of the repeated measures ANOVA is met, that is, the grouping variable has three or more categories, the variable measuring the characteristic of interest is normally distributed, the variable measuring the characteristic of interest is normally distributed with homogeneity of variance among all the groups, the repeated measures ANOVA will measure the differences in the mean questionnaire scores between the four different time points. The repeated measures ANOVA will also detect differences in dependent measures across time and determine variability and probable effect size. The data analysis will be done using ANOVA test, at an alpha level of 0.05. A post hoc analysis will be conducted to determine which of the means are different in order to draw a conclusion on the incidence of chemotherapy related cognitive impairment.
Timeline

[Diagram showing project timeline with various stages and dates]
The concept of impaired cognitive function related to cancer treatment is important as it pertains to understanding the experience of the phenomenon thus expanding the knowledge base for oncology nursing. Understanding the state of the science is imperative in determining the short-term and long-term consequences of cognitive change and its impact on quality of life. This project would allow the opportunity for future oncology nurse researchers in exploring strategies to manage the change. Patients presenting with cognitive complaints need to be assessed to determine appropriate intervention. When the impact of cognitive impairment related to chemotherapy is better understood, appropriate interventions can be developed to manage these cognitive changes and help individuals cope. This project also addresses the ONS research agenda of developing in-depth knowledge of cancer-related symptoms and side effects in order to prepare nurses in educating patients regarding this potential side effect. Lastly, this project involves the assessment of both short-term and long-term cognitive effects of high dose chemotherapy which targets the ONS Research Agenda of “Late Effects of Cancer Treatment and Long-Term Survivorship Issues.” Understanding the cognitive changes that may occur as a result of chemotherapy is imperative for care providers in order to manage, improve, or maintain functional ability in addition to supporting health-related quality of life.
Protection of Human Subjects used for Research

The treating physician specializing in hematology/oncology will share information about the study with eligible patients during a scheduled visit. If a patient expresses interest and gives permission, the referring provider will contact the principal investigator with the patient’s preferred means of initial contact. A meeting will be scheduled in a private quiet room in the patient’s local clinic and a consent form will be reviewed. Once adequately informed, the patient will be asked to sign a consent form that includes a release of clinical information from the patient record regarding clinical characteristics of their disease process and subsequent treatment. Participants for this study will be recruited following the Health Insurance Portability and Accountability Act (HIPAA) guidelines.

Ensuring the patients’ safety particularly in such a vulnerable population is crucial. In addition to ensuring a safe environment, ample amount of time will be provided for patients to complete the questionnaires. A general health and psychosocial assessment will be conducted prior to assessment to ensure patient has the functional ability and energy to complete the series of questions. If a patient is feeling ill or other stressors present, the assessment can be rescheduled to accommodate the patient’s condition. Sufficient time will be provided to reduce the risk of respondent burden. In addition to the patients’ safety, the patients’ privacy and confidentiality will be protected with the use of a locked file cabinet and database management system, all information is to be held in confidentiality in a locked file cabinet in the principle investigator’s office for a minimum of 7 years. Once the surveys are completed, the principal investigator will
replace patient’s name with a code number, which means patient’s real name will not appear on the surveys thereafter. Additionally, no one will have access to this code number except for the PI.

**Women and Minority Inclusion**

The target population will be adult patients with multiple myeloma who will be receiving high-dose melphalan for an autologous stem cell transplant. A nonrandom convenience sample will be selected from patients being treated at one of three oncology clinics within a large health care organization in southern California. Inclusion criteria for this study are adults at least 18 years of age with a diagnosis of multiple myeloma, able to read and understand English, and having ECOG performance status ratings of 0-3. Exclusion criteria include alcohol or drug addiction, having a comorbid condition that may affect cognitive status, such as traumatic brain injury, dementia, multiple sclerosis or psychosis.

Information on the composition of the proposed population in terms of sex/gender and racial/ethnic group are dependent on the population characteristics of the location of each individual clinic. According to the United States Census Bureau for San Diego County in 2013, 49.7 percent of the population were female, 76.6% were White alone, 47.2% of the population were non-Hispanic White, 32.9% were Hispanic or Latino, 11.7% were Asian, 0.6% were Native Hawaiian and Other Pacific Islander, 5.6% were Black or African American, 1.3% were American Indian and 4.2% were of two or more races (United States Census Bureau, 2014). It is important to note that men are slightly more likely to develop multiple myeloma than women and that multiple myeloma is more
than twice as common in African Americans than in white Americans (American Cancer Society, 2015). Taking the general population characteristics into consideration as well as the known gender and racial statistics of multiple myeloma is a good prediction of the sample characteristics of this study.

**Innovation**

The proposed study would bring much value to the understanding of cognitive impairment related to high dose chemotherapy. Although the subject of cognitive problems following chemotherapy is becoming the focus of many studies, much of the literature describes women with breast cancer. This may be due to the good prognosis and survival time in this population allowing for evaluation of concurrent and long-term consequences. Although many contributions have been made to the understanding of the phenomenon by studying patients with breast cancer, the findings from this patient population may not be generalizable to a wide range of cancers (Rodin, 2012). The interpretation of study results has also been limited due to descriptive study designs, small sample sizes, presence of uncontrolled confounding variables and the post-treatment timing of evaluation (Mitchell & Turton, 2011). In addition, most of the research has focused on the effects of standard dose chemotherapy on cognitive function. This multiple time series design will allow for baseline evaluations and will allow for the assessment of short and long term cognitive changes.

Presently, there is not a standard measurement or assessment of cognitive function in individuals with cancer. Some studies have demonstrated a lack of correlation between patient self-report of cognitive dysfunction and consequent performance on
neurocognitive tests (Wefel et al., 2004; Evens & Eschiti, 2009). Additionally, the selection of neuropsychological tests used to measure cognitive change related to chemotherapy lacks consistency (Raffa, 2009) and currently no standardization of neuropsychological tests for this specific population has been established. This study focuses on the patients’ perception of cognitive function and aims to standardize the patient self-report as the gold standard of measurement. When the impact of cognitive impairment related to chemotherapy is better understood, appropriate interventions can be developed to manage and help individuals cope with cognitive changes.

**Facilities and Resources**

The research site for this proposed study will take place in California State University of San Marcos, School of Nursing (SON). The SON is an educational and research facility equipped with the resources necessary to carry out the project such as computers, statistical and data management support, office space and other research equipment.