5-2011

THE ASSOCIATION BETWEEN CANCER-RELATED-FATIGUE, RESPONSE TO FATIGUE TREATMENT, AND CYTOKINES AND THEIR RECEPTORS, IN PATIENTS WITH ADVANCED CANCER

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by

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A

THESIS

Presented to the Faculty of
The University of Texas
Health Science Center at Houston
and
The University of Texas
M. D. Anderson Cancer Center
Graduate School of Biomedical Sciences
in Partial Fulfillment

of the Requirements

For the Degree of

MASTER OF SCIENCE

by

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Houston, Texas

May, 2011

Acknowledgements

I would like to thank my mentors and supervisors, Dr. Eduardo Bruera & Dr. James Reuben, for their wisdom, support and guidance over the past 3 years. I would also like to thank my graduate committee, Dr. Alessandra Ferrajoli, Dr. Dave Balachandran, and Dr. Jonathan Trent for their advice regarding this study. I would like to thank Dr. J Lynn Palmer and Dr. Saroj Vadhanraj for their mentorship and key roles in designing the clinical trial. Finally, I am grateful to all the patients enrolled onto this clinical study, who have in the process helped us to gain a better understanding of new ways to improve the quality of life for patients living with advanced cancer.

Abstract

THE ASSOCIATION BETWEEN CANCER-RELATED-FATIGUE, RESPONSE TO FATIGUE TREATMENT, AND CYTOKINES AND THEIR RECEPTORS, IN PATIENTS WITH ADVANCED CANCER

Publication No._____*

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Background: Inflammation is implicated in the development of cancer related fatigue (CRF). However there is limited literature on the mediators of inflammation (namely), cytokines and their receptors, associated with clinically significant fatigue and response to treatment.

Methods: We reviewed 37 advanced cancer patients with fatigue (≥4/10), who participated in two Randomized Controlled Trials, of anti-inflammatory agents (Thalidomide and Dexamethasone) for CRF. Responders showed improvement in FACIT-F subscale at the end of study (Day 15). Baseline patient characteristics and symptoms were assessed by FACIT-F, ESAS; serum cytokines [IL-1β and receptor antagonist (IL-1RA), IL-6, IL-6R, TNF-α and sTNF-R1 and R2, IL-8, IL-10, IL-17] levels measured by Luminex. Data were analyzed using principal component analysis (PCA) [reporting cumulative variance (variance) for the first four components] to determine their association with fatigue and response to treatment.

Results: Females were 54%. Mean (SD) was as follows for age, 61(14); baseline FACIT (F) scores, 21.4(8.6); ESAS Fatigue item, 6.5(1.9); and FACIT-F

change, 6.4(9.7); ESAS (fatigue) change, -2 (2.41). Baseline median in pg/mL for IL-6, TNF-α, IL-1β were 31.9; 18.9; 0.55, respectively. Change in IL-6 negatively correlated with change in FACIT-F scores (p=0.02). Baseline CRF (FACIT-F score) was associated with IL-6, IL-6R and IL-17, Variance = 78% whereas IL-10, IL-1RA, TNF-α and IL-1β were associated with improvement of CRF, Variance=74%. Conversely, IL-6 and IL-8 were associated with no improvement or worsening of CRF, Variance= 93%.

Conclusions: Change in IL-6 negatively correlated with change in FACIT-F scores. IL-6, IL-6R and IL-17 are associated with CRF while IL-6 and IL-8 were associated with no improvement of CRF. Further studies are warranted confirm our findings.

TABLE OF CONTENTS

Acknowledgements ..... **iii**

Abstract ..... **iv**

List of Tables ..... **ix**

Chapter 1. Introduction **1**

A. Background 1

B. Study Rationale 11

C. Hypotheses 13

D. Study Aims 13

Chapter 2. Research Design and Methods **14**

A. Study Design 14

B. Inclusion Criteria 14

C. Exclusion Criteria 14

D. Patient Screening and Recruitment 15

E. Treatment Plan 17

F. Study Outcome Measures 18

G. Statistical Analyses 21

Chapter 3. Results **23**

Chapter 4. Discussion **29**

Limitations 32

Conclusions..... 33

Appendix 34

A. Study Forms: Memorial Delirium Assessment Scale 34

B. Study Forms: Functional Assessment of Cancer Therapy 38

C. Study Forms: Edmonton Symptom Assessment Scale..... 41

D. Cyokine Assessement and Methods 42

E. Study Consent…….. 47

F. Treatment Plan and Standard operating procedure……. 60

Bibliography 61

Vita ……..71

List of Illustrations

Figure 1. Interaction between various cytokines and hypothalamic –pituitary adrenal axis…….....5

Figure 2. Schematic Diagram Illustrates the Interactions between Tumor, Tumor Byproducts, Brain, Nerves, Cytokines, Symptoms and Anti-Inflammatory Agents (Thalidomide and Dexamethasone).....11

List of Tables

Table A. Corticosteroids (dosage and duration) in the management of Cancer Related Fatigue.....9

Table 1. Patient Characteristics.....24

Table 2. Association of Baseline FACIT-F and Baseline Cytokines.....26

Table 3. Association of Baseline Fatigue Cluster and Baseline Cytokines....26

Table 4. Association of Change in FACIT-F and Change in Cytokines 27

Table 5. Association of Change in Fatigue Cluster and Change in Cytokines...

……...27

Chapter 1. Introduction

A. Background

A. 1. Fatigue in patients with cancer

Fatigue is the most common chronic and severe symptom associated with cancer [1-3]. Fatigue is often the one symptom most likely to interfere with physical and social activities. In cancer patients receiving cancer-related treatment, the frequency of fatigue exceeds 75%. Among the cancer related symptom, fatigue is the most severe symptom and has most profound influence on patients' quality of life [1]; more than 91% of affected patients reported that fatigue interfered with their ability to lead normal lives. Sixty-one percent of patients reported that fatigue affected not only pain but their performance at work; fatigued patients were absent an average of 4.2 days per month during and immediately after treatment, because of fatigue [2]. Despite its effect on all aspects of quality of life, cancer-related fatigue is under-treated or overlooked by oncologists.

A. 2. Fatigue and advanced cancer

Previous research has shown that patients with advanced cancer develop severe physical and psychosocial symptoms as a result of cancer and its treatments. The frequency of cancer-related fatigue (CRF) varies from 60% to 90%. CRF is more severe in advanced stages as compared to early disease stage [4]. CRF can prevent these patients from receiving effective cancer therapy. Despite the

prevalence of CRF, severity and effects on the quality of life of patients with advanced lung cancer, there are limited treatment options available. Prior studies have revealed that CRF has a multifactorial etiology in these patients [5]. Several factors are significantly associated with CRF, including: anxiety, depression, pain, anorexia/cachexia, drowsiness, sleep disturbances, and cognitive functioning [6]. In recent years, several cytokines and other pro-inflammatory mediators, produced by the host in response to the presence of cancer have been found to be associated with symptoms such as fatigue, pain, cognitive impairment, depression, cachexia, and sleep disorders [7-9]. The lack of effective treatment is due to limited understanding of this complex pathophysiology and inability to target the known complex mechanisms of CRF adequately.

A. 3. The Role of Cytokines and fatigue

Origination of the cytokines and general function: Cytokines are polypeptides secreted by the immune cells (T –cells, macrophages) that mediate communication between cells. The immune cells are activated in patients with cancer by cancer, cancer complications and its treatment. The T-cell subsets have a key role in the regulation of inflammatory responses. Immune cells via inflammatory cytokines activate the transcription factor, Nuclear factor- Kappa B [NF-κB], a critical regulator of pro-inflammatory responses. NF-κB can be found in the cytoplasm of all cell types in its inactive form, associated with inhibitory proteins known as inhibitors of NF-κB (IκB). NF-κB is also inactivated by the

induction of IκB that prevents the nuclear translocation of NF-κB and the subsequent transcription of inflammatory cytokines. [10].

Functions of inflammatory cytokines: Interleukin (IL)-1β is a pro-inflammatory cytokine. It belongs to the gene family IL-1α and IL-1 receptor antagonist (IL-1RA). These molecules bind to two receptors (type I and type II). Upon activation by the ligand, the type I receptor complexes with accessory protein, which results in signal transduction. IL-1 along with IL-6 and Tumor necrosis factor–alpha (TNF-α) induce the synthesis of neurotransmitters such as serotonin, Indoleamine 2,3 dioxygenase, p38 mitogen-activated protein kinase, dopamine and glutamine [9]. These neurotransmitters are involved in modulation of symptoms such as fatigue, depression which constitute the sickness behavior. In addition these cytokines modulate pattern of secretion of hypothalamic -pituitary adrenal axis [HPA] secretion that characterizes cancer related fatigue[9]. IL-6 is secreted by T cells and macrophages. It acts as both pro- and anti-inflammatory cytokine. IL-6 exhibits its action via a receptor complex consisting of specific IL-6 receptor and signal transducing subunit(gp130) by a process called trans-signaling[11].

TNF-α is an inflammatory cytokine with primary action via two receptors TNF R1 and TNF R2. Upon contact with a ligand, the TNF receptors form trimers which lead to conformational changes on the receptor leading to activarion of NF-kB, MAPK and induction of death signaling pathways. In conjunction with IL-1β and

IL-6, TNF-α modulate pattern of secretion of neurotransmitter and hypothalmic-pituitary-adrenal axis[HPA] secretion as described earlier.

The interleukin (IL)-10 family of cytokines and the closely related interferon (IFN) family of cytokines form the larger major histocompatabilty complex (Class II cytokine family. IL-10 has strong anti-inflammatory properties by deactivation of macrophages[12]. It downregulates the expression of Th1 cytokines such as interferon –gamma, TNF-α, MHC class II antigens, and costimulatory molecules on macrophages. It enhances B cell survival, proliferation, and antibody production. Its action counter balances the action of elevated IL-1 and/ or TNF-α to maintain homeostasis [13].

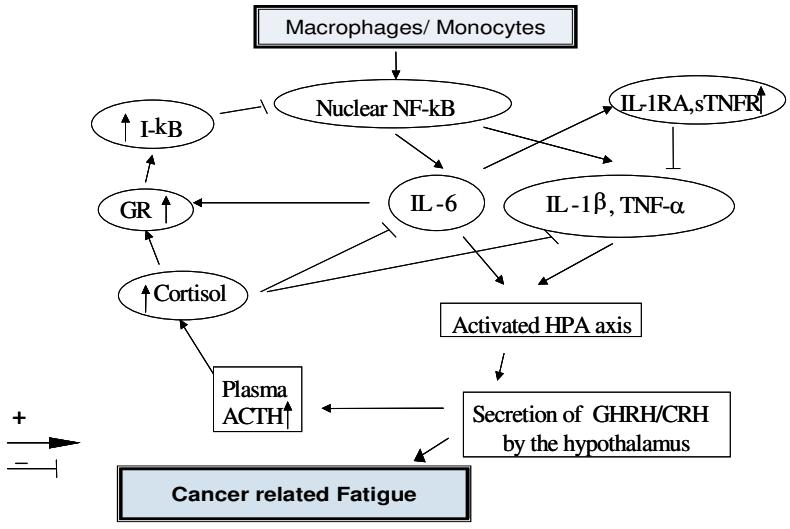
Downstream effects of various cytokines:

The biological functions of the cytokines are achieved by binding with high affinity and specificity to cell surface receptors, thereby triggering signal transduction cascades that regulate cellular function (e.g., activation, proliferation).

The cytokines effects are via tyrosine kinases such as Janus kinase(jaks). The Jaks via its Phosphotyrosine- containing motifs bind to the receptors of signaling proteins including Signal transducers and activators of transcription(STAT) proteins. Upon binding the STAT proteins undergo phoshorylation and dimerization. On transfer to nucleus the STAT proteins bind to the target gene promoters and regulate transcription by binding to CBP protein or p300 co-activator molecules resulting in unwinding of DNA[10].

When an acute inflammatory response is triggered [e.g., Lipopolysaccaride and endotoxin], the immune cells such as macrophages activate the nuclear NF-kB which in turn lead to activation of the IL-1β, IL-6, and TNF-α[See Fig 1]. Finally IL-6 inhibits IL-1β and TNF-α production not only by directly inhibiting the release their synthesis and release [14], but also by stimulating the induction of IL-1β receptor antagonist, IL-1RA, and sTNF-αRI [15]. This action counter balances the action of elevated IL-1 and/ or TNF-α to maintain homeostasis [13]. Interleukins such as IL-6 are pleiotropic and exhibit overlapping function due to sharing of common signal transduction pathways e.g., Functional receptor complexes for interleukin-6 family of cytokines share gp130 as a component critical for signal transduction [14].

Fig. 1. Interaction between various cytokines and hypothalamic –pituitary adrenal axis [Illustration compiled based on the literature review from Schindler et al., Vitkovic, Garg et al. and capuron et al.[9,10,13,and 14]



The pleiotropic and overlap in function of various inflammatory cytokines due to same cell distribution of their receptors and sharing common downstream signaling pathways [10]. For example, following induction of external stimuli, TNF-α and other cytokines such as IL-1β, IL-6, and TNF-α stimulates the production of various inflammatory cytokines such as IL-1, IL-6, IL-8, IFN and TGF-β. By the modulation of receptor expression of one cytokine by other or interactions at the level of signal transduction, gene expression or posttranslational level, the interactions of the cytokines can be synergistic (e.g., TNF-α -IL-1 interactions) or antagonistic (TNF-α and TGF-β) [16]

Prior studies have proposed the role of inflammatory cytokines such as IL-6 in mediation of cancer related fatigue via various mechanisms including: (a) Neuro-endocrine activation the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of Growth hormone releasing hormone (GHRH) and corticotrophin-releasing hormone (CRH) by the hypothalamus [8,9]. Changes in the balance between GHRH and CRH are the principal regulators of CRF. One mechanism by which the cytokine exposure may influence HPA axis function is through inhibitory effects on the receptor for glucocorticoids, cortisol, the end product of HPA axis activation [9] (b) Effects on neurotransmission in the brain: Studies in depression [9], have indicated that inflammatory cytokines effect symptoms such as depression, fatigue by alteration synthesis and uptake of neurotransmitters

such as serotonin, indoleamine 2,3 dioxygenase(IDO), p38 Mitogen activated protein kinase (MAPK), dopamine, and glutamate[9]. One of the mechanism by which inflammatory cytokines alters the secretion of neurotransmitters such as serotonin is by enhancing the activity of serotonin transporter (SERT).

Studies on relationship between cancer-related-fatigue and cytokines:

Cytokines have been associated with the presence of tumors, co-morbidities such as infections and the effects of cancer treatments including radiation therapy and cytotoxic therapy [7-9]. In recent years, it has become evident that many cytokines have powerful effects on the brain [9]. Animal models of symptoms such as pain and cachexia, and clinical studies of immunotherapy in which pro-inflammatory cytokines are administered to patients with various cancers have provided important insights into the central effects of these agents [9].

Sickness behavior [fatigue, depression, sleep alteration] is typically associated with behavioral changes seen in laboratory animals suffering from microbial infections [9,10]. IL-1β, IL-6, TNF-α were found to mediate sickness behavior [9,10]. IL-1β, IL-6, TNF-α is known to cause the symptoms of sickness behavior by it action in the brain, more specifically through the HPA axis [7,8,17,18]. Various studies have shown an association between severity of fatigue and increase in cytokines. Greenberg et al [19] in a longitudinal study for 9 weeks in 15 cancer patients with prostate cancer receiving radiation therapy found a

significant correlation of fatigue with IL-1B. Ahlberg et al. [20] in a longitudinal study in 15 patients with uterine cancer receiving radiation therapy found a significant negative correlation of fatigue with IL-6. Meyers et al.[21] in 54 patients with AML/MDS found significant correlations of IL-1RA and IL-6 with severe fatigue. Rich et al. [18] in 80 advanced colorectal cancer patients found a significantly positive association between fatigue and transforming growth factor (TGF-α). Wang et al. [22] in 62 advanced lung cancer patients receiving radiation therapy found serum IL-6 levels to be related to the increased mean levels of the most severe symptoms (pain, fatigue, disturbed sleep, lack of appetite, sore throat). Inagaki et al. [23] in 46 patients with advanced cancer found plasma IL-6 levels correlated with the fatigue.

A.4. Corticosteroids and fatigue

Dexamethasone is a synthetic glucocorticoid. It exhibits potent anti-inflammatory, immunosuppressant activity with minimal mineralocorticoid properties. The action of dexamethasone on cytokines such as IL-6, IL-1β, IL-8, IL-10 is by its effect on transcription factor NF-κb which is instrumental in activation of multiple genes[25-30]. Corticosteroids are hypothesized to decrease fatigue by decrease of the cytokines IL-1, IL-6, TNF-α [17-23]. IL-1, IL-6, TNF-α are associated with the causation of fatigue [7-9]. Table A. shows various studies in which corticosteroids were used to manage cancer related fatigue.

Table A. **Corticosteroids (dosage and duration) in the management of cancer related fatigue [29-42]**

Author	Number of patients	Treatment Duration (days)	Study Drug*	Equivalent Dexamethasone daily dose (mg)
Della Cuna 1989**	40	56	MP	23
Vecht 1994**	96	28	DM	4-16
Bruera et al 1995**	40	14	MP	6
Popiela et al**	173	56	MP	23
Italian group 2000**	708	5	DM	8
Akira Inoue 2003**	68	6	DM	8
JR Hardy 2001	160	22	DM	12
Mercadante	376	26	DM	4-16
Bruera 2004**	51	7	DM	20

*MP= Methylprednisolone, DM=Dexamethasone
** Randomized, double blind placebo controlled studies

A.5. Thalidomide and fatigue

Studies have identified several side effects of interferon therapy, including flu-like symptoms such as somnolence and cancer related fatigue [9]. Sickness behavior related to cancer treatment often manifests itself through the symptoms of CRF [8-10]. It has been reported that cancer related symptoms such as fatigue, depression are associated with an increase in IL-1, IL-6 and TNF-α [8,9]. Prior studies show that Thalidomide improves symptoms contributing to fatigue including sleep disturbance, anorexia and activity [5,32]. Thalidomide selectively modulates the release of such as TNF-α(inhibits), IL-10(increased production) and other cytokines and may potentially improve CRF [31,32].

A.6. Theoretical construct[Fig.2.]

Previous research has shown that patients with cancer develop severe physical and psychosocial symptoms [33,34]. The prevalence rates of the many different symptoms reported by advanced cancer patients include fatigue 90%, followed by pain 41%-76%, anorexia 85%, depression 33%-40%, anxiety 57%-68%, nausea 24%-90%, constipation 65%, sedation/confusion 46%-60%, and dyspnea 12%-58% [33,34]. Various studies in patients with cancer showed that fatigue usually occurs concurrently with other symptoms namely fatigue, anxiety, depression and sleep disturbance and feeling of wellbeing which conform a symptom cluster (Fatigue cluster) [35]. The brain is the ultimate organ where symptoms are perceived [8,9,and17]. Recent studies showed that cancer patients have a surge of inflammatory cytokines which play a predominant role in the causation of fatigue and its cluster [7]. This change in cytokines occurs as a result of complex interactions between the cancer and the host. It has been noted that inflammatory cytokines can influence the stimulation of afferent nerves at the periphery and some of the central synaptic activity at the dorsal horn and in the brain cortex [9]. Also involved in the causation of fatigue is decreased muscle function, tumor by products and the other symptoms that constitute the cluster i.e., fatigue, anxiety, depression and sleep disturbance [35].

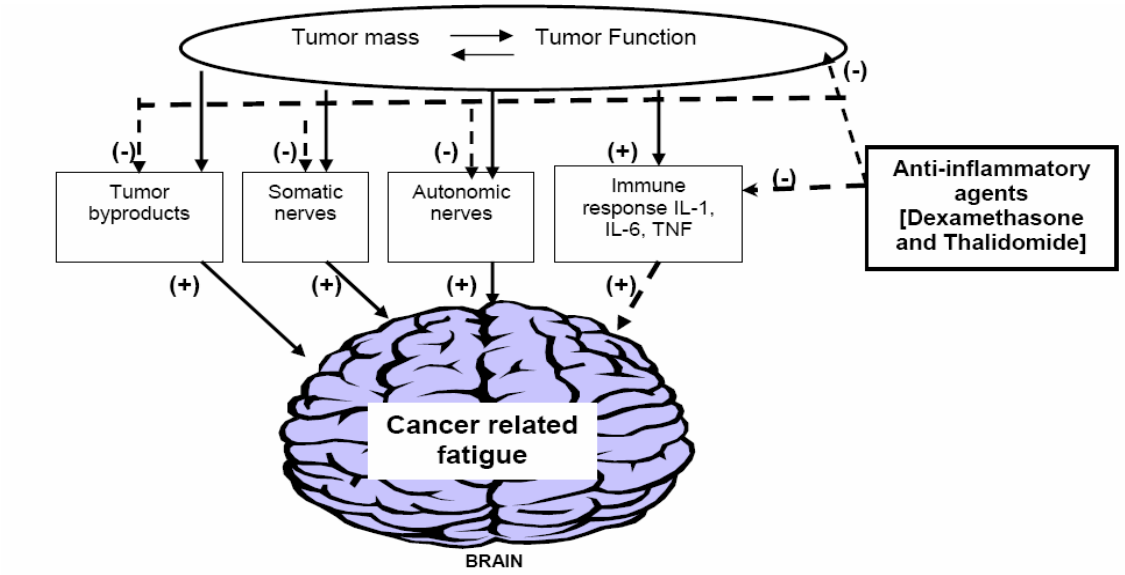


Fig.2.Schematic diagram compiled based on the literature review of Dantzler et al sickness behavior [8,9,17], illustrates the interactions between tumor, tumor by-products, brain, nerves, cytokines, symptoms and anti-inflammatory agents (thalidomide and dexamethasone).

B. Rationale: CRF is the most common distressing and severe symptom in patients with cancer, impacting their quality of life. Unfortunately despite the burden of CRF, there are no proven treatments for it in patients with advanced cancer. The limited treatment options are due to limited understanding of its complex pathophysiology. A number of studies have shown an association between inflammatory markers and fatigue in cancer patients [7-17, 50]. In a pooled analysis of eighteen studies that met the quality criteria, Schubert et al. [7] found a significant positive correlation between CRF and IL-6, IL-1 receptor antagonist (IL-1RA), and neopterin. However, there is limited published data to

show whether improvement in fatigue scores with targeted treatment results in decrease in the elevated levels of inflammatory serum cytokines. As it may not be possible to design a study to investigate the causative role of Inflammatory cytokines for CRF due various confounders such as patient, disease and treatment factors involved, a more feasible design is to investigate the **associations** between change in inflammatory cytokines with treatment of anti-inflammatory agent/s to treat fatigue. The ultimate **goal** is to find treatments for CRF based on targets modulating the inflammatory markers.

The **objective** of this study was to obtain preliminary data to characterize the inflammatory cytokines associated with fatigue in patients with advanced cancer and assess the change inflammatory cytokines with change in fatigue scores with fatigue treatment. The other exploratory objectives were to determine the association of fatigue cluster with various inflammatory cytokines as the manifestation of fatigue occurs concurrently with other symptoms such as anxiety, depression, sleep, and feeling of well-being which collectively constitutes, fatigue cluster. Fatigue cluster is believed to contribute to the symptom burden in patients with advanced cancer which impact quality of life. We also examined the effects of the anti-inflammatory agents (thalidomide, and dexamethasone) on fatigue and the inflammatory cytokines. The preliminary data from this study will be utilized to develop treatment strategies to alleviate fatigue and improve quality of life as well as to help patients to tolerate treatment, in general.

C. The Hypothesis:

I hypothesized that anti-inflammatory agents by their action on inflammatory cytokines are associated with change (decrease) in severity of cancer related fatigue.

Specific Aims:

I planned to test this hypothesis and accomplish the objectives of this project by performing the following specific *aims*:

a) To determine the mediators of inflammation (namely), cytokines (IL-1β, IL-6, IL-8, IL-17, TNF-α and IL-10] and their soluble receptors, associated with clinically significant fatigue s defined as fatigue score of ≥ 4/10 in a o-10 scale.

b) To determine the mediators of inflammation (namely), cytokines (IL-1β, IL-6, IL-8, IL-17, TNF-α & IL-10] and their receptors, associated response to treatment.

CHAPTER II. Research Design and Methods

We accessed the original data for this project from two prospective clinical trials: protocol 2005-0816 Dexamethasone for symptom distress in advanced cancer [NCT00489307] and The Effects of Thalidomide on Symptom Clusters, protocol 2005-0980 in patients with advanced cancer [NCT00379353]. We reviewed the demographic information (such as age, gender, ethnicity, and cancer diagnoses), Edmonton Symptom Assessment System (ESAS), Memorial delirium assessment scale (MDAS), and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores at baseline and day 15. In both the studies, patients who agreed to participate in the study were given a 14-day supply of study medication.

We received approval from The University of Texas MD Anderson Cancer Center Institutional Review Board for the present study and all patients provided written informed consent at the time of their initial enrollments. Due diligence was taken to protect the patients' confidentiality.

Performance Sites

Clinical setting

Patients with advanced cancer were recruited from The University of Texas MD Anderson Cancer Center (MDACC; a comprehensive cancer center), Lyndon B. Johnson General Hospital (LBJ: Harris county hospital) and Four Seasons Hospice and Palliative care, Flat Rock, North Carolina(Four Seasons Hospice). The physicians identified potentially eligible patients to participate in this study.

Research staff

The research staff in the Department of Palliative Care and Rehabilitation Medicine includes a manager of clinical protocol administration, a research nurse supervisor, three research nurses and a data coordinator. Our group has conducted multiple clinical trials related to symptom management, quality of life and communications between patients and physicians.

Patients Screening and Recruitment

Patients with advanced cancer were recruited from MDACC, LBJ and Four Seasons Hospice. Inclusion criteria for the current study included the following: a fatigue score ≥4 on a scale of 0–10 (0 = no fatigue, 10 = worst possible fatigue) during the previous 24 hours; No clinical evidence of cognitive failure as evidenced by MDAS score of ≥13 at baseline or normal MMSE score (that is, a score ≥24); and a hemoglobin level ≥10 g/dL. Exclusion criteria were of use of steroids (including dexamethasone, Megestrol), thalidomide or lenalidomide, neutropenia, sepsis and/or acute, chronic, or ongoing infections, pregnant and lactating women and all major surgeries such as thoractomy, that requires wound healing within last 2 weeks.

Patient rights and confidentiality

Patients were informed that refusing to participate in the study or electing to terminate their participation will not affect their current treatment plan. The patients were given a written and verbal description of the study during the informed consent teaching interview. Guidelines regarding Institutional Review Board, Human Rights Protection were strictly followed.

Study subjects signed an IRB-approved written informed consent form after having the study explained to them in person by a physician. Patients were assured that that lack of participation in the study would not bear a relationship to their care for cancer or its symptoms. Circumstances of obtaining informed consent were documented in patient medical records. Informed consent was obtained in the language preference of the potential subject. When necessary, professional translators, and not family members, were utilized to obtain written informed consent.

We maintained confidentiality by assigning a study number to all study subjects. Data collected was identified and tracked using this number. No names or other identifying information were attached to the data collection.

Screening and accrual process is described in detail below:

a) The research nurse screened the electronic medical records of outpatient center visits of all patients of collaborators for the patients meeting the eligibility criteria.

b) The research nurse notified the Sriram Yennu MD, principal investigator and the collaborator of the eligibility.

c) Eligible patients were approached by the research nurse to obtain consent.

d) Consented patients were enrolled in the study. Reason for inability to consent was documented in the screening log.

e) Weekly protocol meeting chaired by the PI, included the research nurse, research manager, protocol manager, data coordinator to review the screening, accrual, status of the patients on the study including adverse events, serious adverse events, dropouts.

f) Annual review of the data was conducted by the data safety and monitoring board at MD Anderson Cancer Center. The IRB conducted an annual review of the protocol in regards to patient protection, accrual, and adverse events. Department and Intuitional audits were performed in order to ensure data quality.

Study treatment Plan

In the study, consenting eligible patients received study medication for 14 days. Exam (including history including FACIT-F, ESAS and toxicity assessment were

done at baseline, and Day 15 [± 3 days]. Serum cytokines (IL-1β, IL-6, IL-17, TNF-α, IL-10, IL-8, and corresponding receptor levels), on baseline and Day 15 [± 3 days] were collected.

Study Medication strength, frequency:

- The dose of dexamethasone was 8mg a day.
- The dose of Thalidomide is 100mg a day.

Outcome Measures

1. Baseline demographics were collected from each patient and/or health records just prior to initiation of study intervention, and included the following:

- Demographics (date of birth, gender, race)
- Cancer diagnosis (date of diagnosis, cancer type, treatments received)
- Fatigue measures: Functional Assessment for Chronic Illness Therapy-Fatigue (FACIT-F) (see below for details)

Cytokine measures (See below for principles and Method in Appendix D):

Cytokines such as IL-1, IL-6, TNF-α, IL-10, IL-8, IL-17 (serum) and their receptors have been reported to correlate with other symptoms such as fatigue anorexia/cachexia, nausea, pain, depression, cognitive impairment and sleep disorders in cancer patients.

In this study, we measured the levels of IL-1, IL-6, TNF-α, IL-10, IL-8, IL-17 (serum) and their receptors at baseline, days15 [± 3 days]. The serum samples

were stored frozen for subsequent cytokine profile. Serum samples were assayed. The cytokine profiles were correlated with the intensity of symptoms and for the responsiveness or failure to respond to study medication. Pro-inflammatory cytokines IL-1, IL-6, TNF-α, IL-10, IL-8, IL-17 (serum) and their receptors were measured in the serum of patients using commercially available Luminex kit (Biosource Inc.). The Multiplex Bead Immunoassay was being used to measure serum levels of IL-1, IL-6, TNF-α, IL-10, IL-8, IL-17 and their receptors. Serum IL-10, IL-1β, IL-1RA, IL-6R, TNF-RI, TNF-R2 were also analyzed using ELISA, as the data obtained were undetectable levels in majority of study patients using Multiplex Bead Immunoassay.

Measure for Delirium:

- Memorial Delirium Assessment Scale (MDAS) (Appendix A) is a 10 item questionnaire validated in cancer patients for assessment of delirium (51). It can be administered by a physician, a nurse or a research coordinator, assigning a score between 0 and 30. A score of >13 is suggestive of delirium. This measure was used to assess the eligibility to the clinical study, as patients with delirium are not eligible to participate in the study.

Fatigue Measures:

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (Appendix B): The FACIT-F fatigue subscale has been used primarily in cancer patients to measure fatigue (52). The subscale consists of 13 items. Patients rate the intensity of fatigue and its related symptoms on a scale of 0-

4, from 0 “not at all” to 4 “very much”. The scoring is 0-52 points, a higher score (e.g., 48) indicates low intensity of fatigue and a low score (e.g., 11) indicates severe fatigue. Test-retest reliability coefficients for the fatigue subscale have ranged from 0.84-0.90. This scale has demonstrated strong internal consistency (alpha=0.93-0.95). This assessment was performed at baseline, and day 15.

The Edmonton Symptom Assessment System (ESAS) (Appendix C): This tool was designed by our group to assist in the assessment of ten symptoms common in cancer patients: pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feelings of well-being (53,54). The severity at the time of assessment of each symptom is rated from 0 to 10 on a numerical scale, 0 meaning that symptom is absent and 10 meaning that it is of the worst possible severity. The instruments and techniques are both valid and reliable in the assessment of the intensity of symptoms in cancer populations. Symptom assessment was evaluated at baseline, and day 15. Fatigue with other symptoms such as anxiety, depression, sleep disturbance and feeling of wellbeing as assessed by ESAS was used to calculate Fatigue cluster [FADSW] [35].

- **Methods for collection storage analysis and interpretation of cytokines**

  To study the effect(s) of study drug, levels of inflammatory cytokines (interleukin-6 [IL-6], IL-8, IL-17,IL-10, IL-1β, and TNF-α), and cytokine receptors (IL-6R, IL-1RA and soluble TNF-receptors (sTNF-R1, sTNF-R2)

were measured at baseline, and day 15 of treatment in 45 patients who consented for additional blood collections for optional correlative studies.

Collection and Storage of serum

Peripheral blood was drawn from all subjects and serum sample are stored as per protocol [described in detail in Page 55, Appendix D and reference 55].

Principles and Methods of Multiplex Assay: Appendix: D

Statistical Analysis:

Distributions of data were examined by analyzing the data graphically. If the data appeared to be non-normally distributed, then transformations to the data were considered, or non-parametric equivalents of the parametric tests described in the results below were used for analyses.

To determine the relationships between serum cytokines (IL-6, IL-8, and IL-10, IL-1β, IL-17 and TNF-α), and cytokine receptors (IL-6R and soluble TNF-receptors (sTNF-R1, sTNF-R2), IL-1RA and fatigue at baseline and 14 days of treatment, descriptive statistics for each variable were presented in tables. In addition, we correlated cytokines and the fatigue [FACIT-F, ESAS fatigue item]and fatigue cluster score using Spearman correlation coefficients as the data was not normally distributed. We also reported the ratio of IL-6/IL-10 ratio as both these cytokines constitute the predominant pro-inflammatory and anti-inflammatory response, their interaction may play a important role in the clinical

manifestation of symptoms of cancer and its treatment such as fatigue and fatigue clusters, the outcome of our study as evidenced in prior studies in neonates, major surgeries, burns or trauma [56, 57].

We used principle component analysis (PCA) to determine which symptoms cluster together to form a principle component and if other variables, such as cytokines, will also load highly on individual factors. Our goal was to discover the underlying, unobservable factors (latent factors) associated with the interrelationships of these variables. We included analyses of scores at two points in time. Time one is at baseline, when all patients have not yet received study medication; time two will be at day 15. For analyses at time two, we performed PCA in whom we had observed improved fatigue (defined as atleast 1 point improvement in the FACIT-F fatigue scores) and those without improved fatigue. Each PCA included the serum cytokines (interleukin-6 [IL-6], IL-8, and IL-10, IL-1β, and TNF-α), and cytokine receptors [IL-6R and soluble TNF-receptors (sTNF-R1, sTNF-R11)], IL-1RA and the FACIT-F fatigue subscale score.

CHAPTER III. Results

The median age of the 45 patients was 62 years; the most common primary cancers were gastrointestinal and lung. [Table 1]

Table 1.a. shows descriptive data of demographic characteristics, baseline fatigue scores (FACIT-F, Fatigue subscale and ESAS, Fatigue item) and serum inflammatory cytokines levels.

The median change of fatigue at the end of study (primary endpoint) was 6 points (FACIT-F) and -2 points (ESAS-Fatigue item).

Table 1.b. shows that the serum levels of the control subjects was less than fatigued advanced cancer patients. A Mann-Whitney U test determined the difference between the control and fatigue patients of the study to be significant for IL-6, TNF-α, IL-8, IL-17, and IL-1RA. However there was no difference in the levels of IL-1β and IL-10.

Table 2 shows significant association between baseline fatigue as assessed by FACIT-F and ESAS- fatigue item and fatigue cluster (Fatigue, anxiety, depression, sleep disturbance and feeling of well-being). However no association was found between baseline fatigue (FACIT-F) and baseline serum inflammatory cytokines and receptors {IL-6, IL-8, and IL-10, IL-1β, and TNF-α), (IL-6R, IL-1RA and soluble TNF-receptors (sTNF-R1, sTNF-R2)}.

Table 3 shows significant association between baseline fatigue cluster (FADSW) and baseline FACIT-F scores, serum cytokines IL-10, IL-6/IL-10 (pro-inflammatory and anti-inflammatory ratio).

Table 1. a. Patient characteristics(n=45)

Patient characteristics	Mean (SD)	Median
Age	61(14)	62
Sex	Female 54%	
Race		
White	60%	
Hispanic American	6%	
Asian American	26%	
African American	8%	
Primary cancer diagnosis (%)		
Breast	3 (6%)	
Gastrointestinal	11(24%)	
Genitourinary	4 (8%)	
Sarcoma	6(13%)	
Lung/head and neck	10(22%)	
Others [a]	11(24%)	

[a] brain, Lymphoma/myeloma/leukemia, gynecological, no evidence of disease (NED), skin, unknown primary, melanoma.
* **Fatigue, anxiety, depression, sleep disturbance and feeling of well-being cluster**

Table 1.b. Baseline fatigue scores and change in fatigue scores after 14 days of treatment

Fatigue scale (n=45)	Mean(SD)	Median
FACIT-F subscale	21.46(8.68)	22
ESAS – Fatigue item	6.55(1.99)	7
Fatigue cluster (FADSW)*	22.26(8.7)	21
ESAS-F CHANGE	-2(2.41)	-2
FACIT-F CHANGE	6.4(9.73)	6

FACIT-F=Functional assessment of cancer illness therapy- fatigue
ESAS=Edmonton symptom assessment scale
Fatigue cluster= fatigue, anxiety, depression, sleep disturbance and feeling of well-being

1 .c. Baseline cytokine and receptors levels in advanced cancer patients with clinically significant fatigue(n=45

Baseline serum Cytokine and Receptor levels(pg/ml)	Mean(SD)	Median	Range
IL-6	67.57(122)	31.96	
IL-1RA	725.7(542)	547	
TNF-α	32.15(48.6)	18.91	
IL-6R	14697(14780)	8812.5	
IL-1 β	5.7(4.41)	0.55	
IL-8	403.7(1012.2)	82.16	
IL-10	11.77(15.5)	4.9	
TNFR1	1511(973.7)	1309	
TNFR2	6914.6(6196)	5445.6	
IL-17	82.5(165)	22.42	

Table 1.d. Comparison of serum baseline cytokine levels with Normal controls

Serum cytokines	N= normal	Mean(SD) (pg/mL) in normal controls	Median (pg/mL) in normal controls	N=fatigued advanced cancer patients	Mean(SD) (pg/mL) in fatigued advanced cancer patients	Median (pg/mL) in fatigued advanced cancer patients	P-value*
IL-6	52	14.3(21)	7.08	45	67.57(122)	31.9	<0.001$^{\Psi}$
TNF-α	42	14.6(50.9)	5.9	45	32.15(48.6)	18.9	<0.001$^{\Psi}$
IL-8	42	30.3(36.7)	16.7	45	403.7(1012)	82.1	<0.001$^{\Psi}$
IL-17	42	30(58)	7.2	45	82.5(165)	22.4	0.03$^{\Psi}$
IL-1RA	19	265(139)	231	39	725.7(542),	547	0.01$^{\Psi}$
IL-1β	8	19.5(42.3)	3.4	34	5.7(4.41)	0.55	0.65
IL-10	15	50.5(137.3)	2.9	38	11.77(15.5)	4.9	0.48

* Mann-Whitney U test (two-tailed),
$^{\Psi}$ A Mann-Whitney U test showed this difference to be significant.

Table 2. Association of Baseline FACIT-F and Baseline Cytokines

Change in variables with Treatment	r	P-value
FACIT-F	**-0.30**	**0.04**
Fatigue(ESAS)	**0.48**	**0.001**
IL-6	-0.20	0.18
IL-1RA	-0.02	0.86
TNF-α	-0.05	0.74
IL-6R	-0.13	0.38
IL-1β	-0.14	0.40
IL-8	0.14	0.34
IL-10	**0.34**	**0.02**
TNFR1	-0.16	0.28
TNFR2	**-0.26**	**0.07**
IL-17	0.13	0.40
IL6/IL10RATIO	**-.47**	**0.002**

***Fatigue, anxiety, depression, sleep disturbance and feeling of well-being cluster**

Table 3. Association of Baseline fatigue cluster and Baseline cytokines

Change in variables with Treatment	r	P-value
Fatigue(ESAS)	**-0.49**	**0.001**
Fatigue cluster(FADSW*)	-**0.30**	**0.04**
IL-6	-0.05	0.55
IL-1RA	0.04	0.77
TNF-α	0.07	0.63
IL-6R	0.07	0.63
IL-1β	0.21	0.21
IL-8	-0.1	0.51
IL-10	0.14	0.38
TNFR1	-0.04	0.76
TNFR2	0.05	0.73
IL-17(L)	-0.09	0.53
IL6/IL10 ratio	0.04	0.80

Table 4. Association of change in FACIT-F and change in cytokines

Change in variables with Treatment	r	P-value
Fatigue(ESAS)	-0.44	**0.002**
IL-6	0.08	0.56
IL-1RA	-0.24	0.88
TNF-α	0.01	0.90
IL-6R	-0.12	0.52
IL-1β	-0.26	0.15
IL-8	-0.06	0.67
IL-10	0.14	0.59
TNFR1	**0.39**	**0.07**
TNFR2	0.17	0.24
IL-17(L)	-0.15	0.34
IL6/IL10RATIO	-0.14	0.38
ESAS-F CHANGE	0.63	0.0001
FACIT-F CHANGE	-0.396	**0.007**

* **Fatigue, anxiety, depression, sleep disturbance and feeling of well-being cluster**

Table 5. Association of change in fatigue cluster and change in cytokines

Change in variables with Treatment	r	P-value
Fatigue(ESAS)	-0.44	**0.002**
FADSW*	-0.39	**0.007**
IL-6	**-0.34**	**0.02**
IL-1RA	0.14	0.37
TNF-α	-0.20	0.17
IL-6R	0.22	0.13
IL-1β	0.26	0.16
IL-8	-0.24	0.37
IL-10	0.16	0.34
TNFR1	-0.22	0.16
TNFR2	-0.19	0.33
IL-17	-0.05	0.78
IL6/IL10RATIO	-0.14	0.40

* **Fatigue, anxiety, depression, sleep disturbance and feeling of well-being cluster**

Table 4 shows change in fatigue was significantly associated with change in the levels of serum IL-6 levels after treatment for 15 days. However none of the change in serum levels of other inflammatory cytokines was associated with change in fatigue after treatment.

Table 5 shows none of the change in serum levels of other inflammatory cytokines was associated with change in fatigue cluster after treatment. TNFRI was positively correlated with fatigue cluster with trends towards statistical significance($r=0.39$, $p=0.07$). Also interestingly the change in the fatigue scores as assessed by FACIT-F is associated with change in fatigue cluster scores.

Exploratory principal component analysis reporting the 1st 4 principal components (minimum .50 correlation) shows, baseline CRF (FACIT-F score) was associated with IL-6, IL-6R and IL-17, Variance = 78% whereas IL-10, IL-1RA, TNF-α and IL-1β were associated with improvement of CRF, Variance=74%. Conversely, IL-6 and IL-8 were associated with no improvement or worsening of CRF, Variance= 93%.

CHAPTER IV. Discussion:

The preliminary findings in this study show the effect of the key mediator for pro-inflammatory activity cytokine, IL-6 on CRF in patients with advanced cancer. With treatment of CRF for 2 weeks, the change in IL-6 negatively correlated with change in CRF [as assessed using a FACIT-F subscale scores] ($p=0.02$).

In our study, baseline CRF scores [FACIT-F subscale] in advanced cancer patients were associated with serum levels of IL-6, IL-6R and IL-17 as measured by principal component analysis. With treatment of CRF for 2 weeks, serum levels of IL-10, IL-1RA, TNF-α and IL-1β were associated with improvement of CRF. Conversely, serum levels of IL-6 and IL-8 were associated with no improvement or worsening of CRF.

Findings in our study show increased serum levels of pro-inflammatory cytokines with CRF at baseline. These findings are similar to other studies that have shown increased serum levels of inflammatory markers in fatigued cancer patients before treatment onset and during treatment such as chemotherapy and radiotherapy [7, 8, and 50]. In this study we found increased levels of serum cytokines IL-6, TNF-α, IL-8, IL-17, and IL-1RA in study patients compared to control group [Table 1.d]. However there was no significant difference in the IL-1β and IL-10 levels in advanced cancer patients compared to control group. This may be due to a methodological issue with IL-1β assay, as most of the IL-1β is in the bound form and adequate levels of the IL-1β cannot be detected. Therefore IL-1RA may be a more reliable measure of serum IL-1 levels [7]. IL-10 is both an

anti and pro-inflammatory cytokine and hence a variable association with fatigue scores. Future larger sample studies with advanced cancer patients with no fatigue as another cohort is required to validate these important findings.

However In this study there was no direct correlation between baseline fatigue scores and baseline serum levels of cytokines. This may be (a) due to the fact that they had moderate to severe fatigue prior to fatigue treatment, (b) lack of data of serum cytokine levels in patients with advanced cancer with no fatigue. (c) Small sample size, and (d) other interactions at baseline such as cancer type and prior treatment received may have influence the association between fatigue scores and cytokines.

Fatigue is one of the most common and distressing symptoms of cancer and its treatment [1-4]. However there are no proven pharmacological treatments available to date [58,59]. One main reason is lack of characterization and understanding the pathophysiology of CRF [5,7]. As per the current NCCN guidelines [60], most studies to date fail to identify the target mechanism. Based on the results from our study, a larger study to investigate cytokines IL-6, IL-8, IL-10, IL-1RA, TNF-α and IL-1β as one of the key target mechanism/common denominator is warranted.

We observed a median of 6 point improvement in fatigue scores [FACIT-F subscale] after 14 days of treatment. This improvement is above the minimal

clinically important difference [MICD] in fatigue score [MICD using FACIT-F scores is 3.5points] [61].

Fatigue as measured by FACIT-F fatigue subscale scores correlated with fatigue measured ESAS Fatigue item and fatigue cluster (or overall fatigue burden) ($p<0.05$). Moreover, the change in fatigue over time as measured by FACIT-F correlated with the change fatigue measured ESAS Fatigue item and fatigue cluster (or overall fatigue burden) ($p\leq0.007$). These findings validate the findings of a previous study showing the association between fatigue and fatigue clusters [35].

The findings from this study are important as there are no published data showing a change in the cytokines with change in CRF with fatigue treatment in patients with advanced cancer [7-17]. A pilot work by Monk et al. [62] found etanercept, a TNF inhibitor, treatment in solid cancer patients resulted in improved fatigue. However the limitation of the study is small sample size and lack of data and analysis showing the change in fatigue was due to change in serum cytokines levels such as IL-1β, IL-6 or TNF-α.

Another important finding in the study is the association of fatigue cluster with serum cytokines IL-10, IL-6/IL-10 (pro-inflammatory and anti-inflammatory ratio). In addition, we found that a change in fatigue cluster was significantly associated with change in the levels of serum TNF R1 receptor levels after treatment for 14 days. However the low significance levels ($p=0.07$) may be due to the small

sample size. These findings provide preliminary hypothesis-generating data regards to relationship between cytokines constituting the net inflammatory burden and net fatigue burden (as defined in terms of fatigue cluster). Further studies are needed to validate these findings which may result in finding treatments to relieve the net fatigue burden and thus improve quality of life in these distressed patients. Future studies should also consider combined anti-cytokine agents targeting various cytokines with complementary downstream signaling pathways that modulate inflammation. This combined modality may then reduce the possibility of redundancy, thereby a more sustained control of inflammatory cytokines and possible effective improvement of CRF.

Limitations

This study has several limitations. First, the small sample size may have resulted in lack of significant association between FACIT-F subscale scores and IL-6, IL-8, IL-17, IL-10, IL-1β, TNF-α or their receptors at baseline. Second, as the dexamethasone study is currently ongoing (121/125 accrued so far), we are unable to provide the results of the correlation of the inflammatory cytokines with the treatment (dexamethasone or thalidomide) and placebo. We were only able to report the change in the inflammatory cytokines with or without improvement of CRF in addition to the baseline characteristics of fatigue and cytokines in these cohort of advanced cancer patients. However the process of design, methods used for the assessment of symptoms and analysis of cytokines were strictly followed as per protocol. On conclusion of the dexamethasone trial I will be able

to analyze the effect of anti-cytokine agents (dexamethasone or thalidomide) on cytokines and fatigue as compared to placebo and publish the results of the data of all study patients. Thirdly, fluctuation of cytokine levels and intensity of fatigue is common in cancer patients. As only one assessment of fatigue and single blood sample was performed at a time point in our study, future studies could consider use of multiple blood sampling at different times of the day as well as multiple daily assessments of fatigue [7].

Conclusion:

Based on the preliminary analyses CRF score and serum inflammatory cytokines of advanced cancer patients, the change in IL-6 negatively correlated with change in CRF scores after fatigue treatment. With treatment of CRF for 2 weeks, serum levels of IL-10, IL-1RA, TNF-α and IL-1β were associated with improvement of CRF. Conversely, serum levels of IL-6 and IL-8 were associated with no improvement or worsening of CRF. These findings provide important preliminary data regards to the role of various inflammatory cytokines have on causation of CRF. Future studies are warranted to validate these findings using a larger sample so as to develop treatment strategies that target specific cytokines that are known to mediate the causation of CRF.

Appendix: A

Memorial Delirium Assessment Scale (MDAS)

INSTRUCTIONS: Rate the severity of the following symptoms of delirium based on current interaction with subject
Or assessment of his/her behavior or experience over past several hours (as indicated in each time.)

ITEM 1-REDUCED LEVEL OF CONSCIOUSNESS (AWARENESS): Rate the patient's current awareness of and
Interaction with the environment (interviewer, other people/objects in the room; for example; ask patients to
Describe their surroundings).
☐ 0: none (patient spontaneously fully aware of environment and interacts appropriately)
☐ 1: mild (patient is unaware of some elements in the environment, or not spontaneously interacting
appropriately with the interviewer; becomes fully aware and appropriately interactive when
prodded strongly; interview is prolonged but no seriously disrupted)
☐ 2: moderate (patient is unaware of some or all elements in the environment, or not spontaneously interacting
with the interviewer; becomes in completely aware and inappropriately interactive when prodded
strongly: interview is prolonged but not seriously disrupted)
☐ 3: severe (patient is unaware of all elements in the environment with no spontaneous interaction of
awareness of the interviewer, so that the interview is difficulty-to-impossible even with maximal
prodding

ITEM 2-DISORENTATION: Rate current state by asking the following 10 orientation items: date, month day, year,
Season, floor, name of hospital, city, state, and country.
☐ 0: none (patient knows 9-10 items)
☐ 1: mild (patient knows 7-8 items)
☐ 2: moderate (patient knows 5-6 items)
☐ 3: severe (patient know no more than 1 item)

ITEM 3-SHORT-TERM MEMORY IMPAIRMENT: Rate current state by using repetition and delayed recall of 3 words [patient must immediately repeat and recall words 5 min later after an intervening task. Use alternate sets of 3 words for successive evaluations (for example, apple, table, tomorrow, sky, cigar, justice)].

☐ 0: none (all 3 words repeated and recalled)
☐ 1: mild (all 3 repeated, patient fails to recall 1)
☐ 2: moderate (all 3 repeated, patient fails to recall 23)
☐ 3: severe (patient fails to repeat 1 or more words)

ITEM 4-IMPAIRED DIGIT SPAN: Rate current performance by asking subjects to repeat first 3, 4, then 5 digits

Forward and then 3, then 4 backwards; continue to the next step only if patient succeeds at the previous one.

☐ 0: none (patient can do at least 5 numbers forward and 4 backward)
☐ 1: mild (patient can do at least 5 numbers forward and 3 backward)
☐ 2: moderate (patient can do 4-5 numbers forward, cannot do 3 backward)
☐ 3: severe (patient can no more than 3 numbers forward)

ITEM 5-REDUCED ABILITY TO MAINTAIN AND SHIFT ATTENTION: As indicated during the interview by

Questions needing to be rephrased and/or repeated because patient's attention wanders, patient loses track,

Patient is distracted by outside stimuli or over-absorbed in a task.

☐ 0: none (none of the above, patient maintains and shifts attention normally)
☐ 1: mild (above attentional problems occur once or twice without prolonging the interviews)
☐ 2: moderate (above attentional problems occur often, prolonging the interview without seriously disrupting it)
☐ 3: severe (above attentional problems occur constantly, disrupting and making the interview
difficult-to-impossible

ITEM 6-DISORGANIZED THINKING: As indicated during the interview by rambling irrelevant, or incoherent

Speech, or by tangential, circumstantial, or faculty reasoning. Ask patient a some a somewhat complex question (for example, "Describe your current medical condition").

☐ 0: none (patient's speech is coherent and goal-directed)
☐ 1: mild (patient's speech is slightly difficult to follow: responses to questions are slightly off target but not
so much as to prolong the interview)
☐ 2: moderate (disorganized thoughts or speech are clearly present, such that interview is prolonged but not
disrupted)
☐ 3: severe (examination is very difficult or impossible due to disorganized thinking or speech)

Appendix 1
Memorial Delirium Assessment Scale (MDAS)[o 1996]

ITEM 7-PERCEPTUAL DISTURBANCE: Misperceptions, illusions, hallucinations inferred from inappropriate
behavior during the interview or admitted by subject, as well as those elicited from nurse/family/chart accounts of
the past several hours or of the time since last examination:

☐ 0: none (no misperceptions, illus9ions, or hallucinations)
☐ 1: mild (misperceptions or illusions related to sleep, fleeting hallucinations on 1-2 occasions without
inappropriate behavior)
☐ 2: moderate (hallucinations or frequent illusions on several occasions with minimal inappropriate behavior
that does not disrupt the interview)
☐ 3: severe (frequent or intense illusions or hallucinations with persistent inappropriate behavior that
disrupts the interview or interferes with medical care)

ITEM 8-DELUSIONS: Rate decisions inferred from inappropriate behavior during the interview on admitted by the patient, as well as delusions elicited from nurse/family/chart accounts of the past several hours of the time

Since the previous examination.

☐ 0: none (no evidence of misinterpretations on delusions)
☐ 1: mild (misinterpretation or suspiciousness without clear delusional ideas or inappropriate behavior)
marginally disrupt the interview of interfere with medical care)
☐ 2 moderate (delusions admitted by the patient or evidenced by his/her behavior that do not or only
marginally disrupt the interview or interfere with medical care)
☐ 3: severe (persistent and/or intense delusions resulting in inappropriate behavior, disrupting the interview
or seriously interfering with medical care)

ITEM 9-DECREASED OR INCREASED PSYCHOMOTOR ACTIVITY: Rate activity over past several hours, as well as activity during interview by circling (a) hypoactive, (b) hyperactive, or (c) elements of both present.

☐ 0: none (normal psychomotor activity)
☐ a b c 1: mild (hypoactivity is barely noticeable , expressed as lightly slowing of movement. Hyperactive is
barely noticeable or appears as simple restlessness.
☐ a b c (Hypoactivity is undeniable, with marked reduction in the number of movements or marked
2: moderate slowness of movement, subject rarely spontaneously moves or speaks. Hyperactivity is
undeniable, subject moves almost constantly; in both cases, exam is prolonged as a

consequence.)
☐ a b c 3: severe (Hypoactivity is severe, patient does not move or speak without prodding or is catatonic.
Hyperactivity is severe, patient is constantly moving, overreacts to stimuli, requires surveillance
and/or restraint, getting through the exam is difficult or impossible .)

ITEM 10-SLEEP-WAKE CYCLE DISTURBANCE (DIORDER OF AROUSAL): Rate patient's ability to either sleep
Or stay awake at the appropriate times. Utilize direct observation during the interview, as well as reports from
Nurses, family, patient, or charts describing sleep-wake cycle disturbance over the past several hours or since last
Examination. Use observations of the previous night for morning evaluations only.
☐ 0: none (at night sleeps well; during the day, has no trouble staying awake)
☐ 1: mild (mild deviation from appropriate sleepfulness and wakefulness states at night, difficulty falling
asleep or transient night awakenings, needs medication to sleep well; during the day, reports
periods of drowsiness or, during the interview, is drowsy but can easily awaken him/
herself)
☐ 2: moderate (moderate deviations from appropriate sleepfulness and wakefulness states at night, repeated and
prolonged night awakening, during the day, reports of frequent and prolonged napping or,
during the interview, can only be roused to complete wakefulness by strong stimuli)
☐ 3: severe (severe deviations from appropriate sleepfulness and wakefulness states, at night, sleeplessness
during the day, patient spends most of the time sleeping or during the interview cannot be
roused to full wakefulness by any stimuli)

Appendix: B

Name: _____ MRN: _____

FACIT-F (Version 4)

Date: _____ Protocol: _____

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Patient Signature: _____

Name: _____ MRN: _____

FACIT-F (Version 4)

Date: _____ Protocol: _____

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Patient Signature: _____

Name: _____ MRN: _____

FACIT-F (Version 4)

Date: _____ Protocol: _____

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An 12	I am too tired to eat	0	1	2	3	4
An 14	I need help doing my usual activities	0	1	2	3	4
An 15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An 16	I have to limit my social activity because I am tired	0	1	2	3	4

Patient Signature: _____

Appendix: C

Participant's Initials: _____ Acc#:_____ Date: ____/____/____

Edmonton Symptom Assessment System (ESAS)

Please circle the number that best describes your symptoms in the last 24 hours:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Pain Imaginable
No Fatigue	0	1	2	3	4	5	6	7	8	9	10	Worst Fatigue Imaginable
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Nausea Imaginable
No Depression	0	1	2	3	4	5	6	7	8	9	10	Worst Depression Imaginable
No Anxiety	0	1	2	3	4	5	6	7	8	9	10	Worst Anxiety Imaginable
No Drowsiness	0	1	2	3	4	5	6	7	8	9	10	Worst Drowsiness Imaginable
No Shortness Of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Shortness of Breath Imaginable
Best Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Appetite Imaginable
Best Feeling Of Well-being	0	1	2	3	4	5	6	7	8	9	10	Worst Feeling of Well-being
Other Problem	0	1	2	3	4	5	6	7	8	9	10	Worst Imaginable

Signature: _____

Appendix: D

METHODS OF CYTOKINE ASSESSMENT

Serum preparation

Collect whole blood in a preservative-free and anticoagulant free (red top) Vacutainer tube (Becton-Dickinson). After collection of the whole blood, allow the blood to clot by leaving it undisturbed at room temperature. This usually takes 15-30 minutes. Remove the clot by centrifuging at 1,000-2,000 x g for 10 minutes in a refrigerated centrifuge. The resulting serum supernatant is immediately transferred into a clean polypropylene tube using a Pasteur pipette. The samples should be maintained at 2-8℃ while handling. If the serum is not analyzed immediately, the serum will be apportioned into 0.5 mL aliquots in a Nunc cryovial and stored and transported at –20℃ or lower. It is important to avoid freeze/thaw cycles because this is detrimental to many serum components. Samples that are hemolyzed, icteric, or lipemic can invalidate certain tests, and may need to be re-collected. All serum samples were frozen at –80 °C until ready to assay them in batch. The frozen serum samples were be rapidly thawed and brought to room temperature just before they are to be assayed for cytokines. .

Determination of Cytokines by Luminex Multiplex Cytometric Bead Array Assay

Principles of the Method

- Beads of defined spectral properties conjugated to analyte specific capture antibodies and samples (including standards of known analyte concentration, control specimens, and unknowns) are pipetted into the wells of a filter bottom micro titer well plate and incubated for 2 hours.
- During this first incubation, analytes bind to the capture antibodies on the beads. After washing the beads, analyte-specific biotinylated detector antibodies are added and incubated with the beads for 1 hour.
- During the second incubation, the analyte-specific biotinylated detector antibodies recognize their epitopes and bind to the appropriate immobilized analytes. After removal of excess biotinylated detector antibodies, streptavidin conjugated to the fluorescent protein, R-Phycoerythrin (Streptavidin-RPE), is added and incubated for 30 minutes.
- During this final incubation, the Streptavidin-RPE binds to the biotinylated detector antibodies associated with the immune complexes on the beads, forming a four-member solid phase sandwich.
- After washing to remove unbound Streptavidin-RPE, the beads are analyzed with the Luminex 100™ instrument. By monitoring the spectral properties of the beads and the amount of associated R-

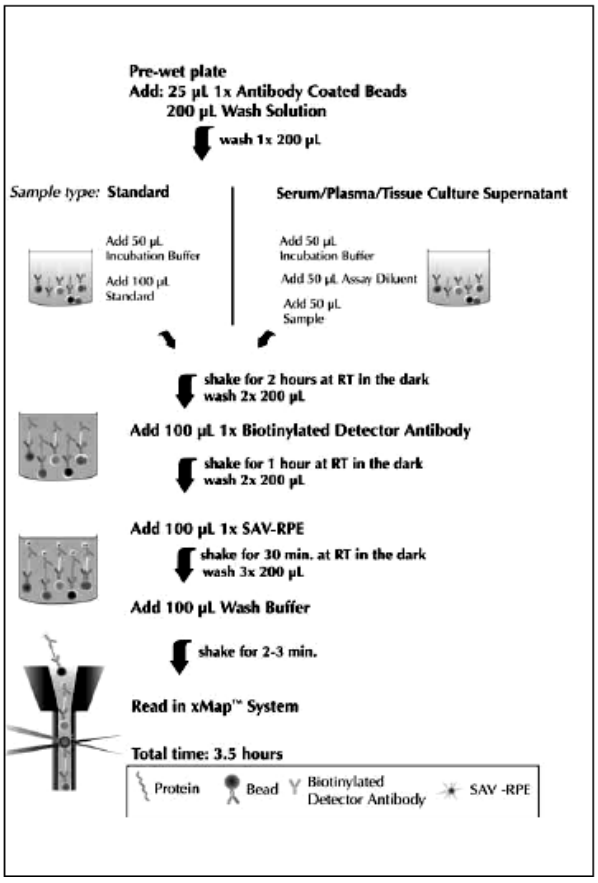
Phycoerythrin (RPE) fluorescence, the concentration of one or more analytes can be determined.

Preparation of Standard

Reconstitute the protein standard within one hour of performing the assay. All standards are calibrated to NIBSC preparations, when available. Additional standards are available from BioSource, Carlsbad, CA. The standard included in the kit is provided as a premixed set of related markers. The concentrations of the protein components of the standard are indicated on the information sheet included in the kit. Standard dilutions may be performed in glass or plastic tubes. When using serum or plasma samples, reconstitute the standard with Assay Diluent provided. Protein standards may be analyzed alone, or may be combined with other protein standards for higher levels of multiplexing.

Assay Procedure **(Figure A, adapted from BioSource™, Invitrogen, Carlsbad, CA)**

Fig A. Multiplex Assay Procedures(Adapted from Biosource, Invitrogenm Carlsbe, CA)



1. Pre-wet the wells designated for the assay. Pipette 0.2 mL of Working Wash Solution into designated wells. Wait 15 to 30 seconds then aspirate the Working Wash Solution from the wells using the vacuum manifold. Wells not used during the assay should be kept dry for future use. An adhesive plate cover may be used to seal the unused wells.
2. Vortex the diluted bead solution for 30 seconds, then sonicate for at least 30 seconds immediately prior to use in the assay.
3. Pipette 25 µL of the diluted bead solution into each well. Once the beads are added to the plate, keep the plate shielded from light.
4. Add 0.2 mL Working Wash Solution to the wells. Allow the beads to soak for 15 to 30 seconds, and then remove the Working Wash Solution from the wells by aspiration with the vacuum manifold. Repeat this washing step. Blot residual liquid from the bottom of the plate on clean paper towels.
5. Pipette 50 µL Incubation Buffer into each well.
6. To the wells designated for the standard curve, pipette 100 µL of appropriate standard dilution.
7. To the wells designated for the sample, pipette 50 µL Assay Diluent followed by

50 µL sample.

8. Incubate the plate for 2 hours at room temperature on an orbital shaker. Shaking should be sufficient to keep beads suspended during the incubation (500-600 rpm).
9. Ten to fifteen minutes prior to the end of this incubation, prepare the biotinylated detector antibody in accordance with instruction.
10. After the 2 hour capture bead incubation, remove the liquid from the wells by aspiration with the vacuum manifold. Add 0.2 mL Working Wash Solution to the wells. Allow the beads to soak for 15 to 30 seconds, then aspirate with the vacuum manifold. Repeat this washing step. Blot residual liquid from the bottom of the plate on clean paper towels.
11. Add 100 µL of 1x stock, diluted Biotinylated Detector Antibody to each well and incubate the plate for 1 hour at room temperature on an orbital shaker. Shaking should be sufficient to keep the beads suspended during incubation (500-600 rpm).
12. Ten to fifteen minutes prior to the end of the detector incubation step, prepare the Streptavidin-RPE in accordance with instruction.
13. Remove the liquid from the wells by aspiration with the vacuum manifold. Add 0.2 mL Working Wash Solution to the wells. Allow the beads to soak for 15 to 30 seconds, then aspirate with the vacuum manifold. Repeat this washing step. Blot residual liquid from the bottom of the plate on paper towels.
14. Add 100 µL of 1x stock, diluted Streptavidin-RPE to each well and incubate the plate for 30 minutes at room temperature on an orbital shaker. Shaking should be sufficient to keep the beads suspended during incubation (500-600 rpm).
15. Prepare the Luminex 100 instrument during this incubation step.
16. Remove the liquid from the wells by aspiration with the vacuum manifold. Wash the beads by adding 0.2 mL Working Wash Solution to the wells; allow the beads to soak for 10 seconds, then aspirate with the vacuum manifold. Repeat this washing step two additional times for a total of 3 washes.
17. Add 100 µL of Working Wash Solution to each well. Shake the plates on an orbital shaker (500-600 rpm) for 2-3 minutes to resuspend the beads. If the plates cannot be read on the day of the assay, they may be covered and stored in a dark location overnight at 2 °C to 8 °C for reading the following day without significant loss of fluorescent intensity. Aspirate Working Wash Solution from stored plates and add 100 µL fresh Working Wash Solution. Place the plate on an orbital shaker 2-3 minutes prior to analysis.
18. Uncover the plate; insert the plate into the XY platform of the Luminex 100 instrument, and analyze the samples.
19. Determine the concentration of samples from the standard curve using curve-fitting software. The four-parameter algorithm usually provides the best fit.

Measurement of Serum Cytokines by ELISA

Principle of the assay

- This assay employs the quantitative sandwich enzyme immunoassay technique. Each well of the 96 wells of a micro titer well plate is pre-coated with a monoclonal antibody specific for a cytokine.
- Standards and samples are pipetted into the wells and the immobilized antibody binds the particular cytokine.
- After washing away any unbound substances, an enzyme-linked monoclonal antibody specific for a cytokine is added to the wells.
- Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of cytokine bound in the initial step.
- The color development is stopped and the intensity of the color is measured. The concentration of the analyte is directly proportional to the intensity of the color of the enzymatic reaction.

Assay procedure

1. Warm up all reagents, working standards, and samples to room temperature.
2. Add 50 μL of Assay Diluent to each well.
3. Add 200 μL of Standard, control, or sample per well. Cover with the adhesive strip provided with the kit. Incubate for 2 hours at room temperature.
4. Aspirate each well and wash, repeating the process three times for a total of four washes. Wash each well by filling each well with Wash Buffer (400 μL) using a squirt bottle, manifold dispenser or automatic washer. Complete removal of liquid at each step is essential to good performance. After the last wash, remove any remaining Wash Buffer by aspirating or decanting. Invert the plate and blot it against clean paper towels.
5. Add 200 μL of Conjugate to each well. Cover with a new adhesive strip.
6. Incubate for 2 hours at room temperature.
7. Repeat the aspiration/wash as in step 5.
8. Add 200 μL of Substrate Solution to each well. Protect from light. Incubate for 30 minutes at room temperature.
9. Add 50 μL of Stop Solution to each well. If color change does not appear uniform, gently tap the plate to ensure thorough mixing.
10. Determine the optical density of each well within 30 minutes, using a microplate reader set to 450 nm. If wavelength correction is available, set to 540 nm or 570 nm. If wavelength correction is not available; subtract readings at 540 nm or 570 nm from the readings at 450 nm. This subtraction will correct for optical imperfections in the plate. Readings made directly at 450 nm without correction may be higher and less

accurate.

11. Create a standard curve by reducing the data using computer software capable of generating a four parameter logistic (4-PL) curve-fit. As an alternative, a standard curve will be constructed by plotting the mean absorbance for each standard on the y-axis against the concentration on the x-axis and drawing a best-fit curve through the points on the graph. Plotting the log of cytokine concentrations versus the log of optical density (OD) may linearize the data, and the best-fit line can be determined by regression analysis. This procedure produces an adequate but less precise fit of the data. If samples have been diluted, concentrations read from the standard curve will be multiplied by the dilution factor.

Appendix: E

Study consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

The Effect of Dexamethasone on Symptoms in Patients with Advanced Cancer
2005-0816

Study Chair: Sriram Yennurajalingam

1.

Participant's Name Medical Record Number

You are being asked to take part in this clinical research study at The University of Texas M. D. Anderson Cancer Center ("M. D. Anderson"). This consent form explains why this research study is being done and what your role will be if you choose to take part. This form also describes the possible risks connected with being in this study. After reviewing this information with the person responsible for your enrollment, you should know enough to be able to make an informed decision on whether you want to take part in the study.

You are being asked to take part in this study because you have advanced cancer and are experiencing weight loss, fatigue, pain, nausea, loss of appetite, sleep problems, and/or depression.

DESCRIPTION OF RESEARCH

2. PURPOSE OF STUDY

The goal of this clinical research study is to learn if dexamethasone can help to control symptoms such as fatigue, pain, nausea, weight loss, loss of appetite, sleep problems, and/or depression in patients with advanced cancer.

Optional Procedures: You will be asked to allow blood to be drawn for tests to study how levels of certain proteins in your blood (called cytokines), white blood cells (called monocytes) and cell receptors for these proteins are affected by taking dexamethasone and how this may change the symptoms you have.

You are being asked to complete a questionnaire on the quality of your sleep.

You are being asked to give saliva samples to check your level of cortisol. Cortisol is a hormone that may be affected by sleep pattern changes.

3. DESCRIPTION OF STUDY

Dexamethasone decreases inflammation and also suppresses the immune system.

Before you can start treatment on this study, you will have what are called "screening tests". These tests will help the doctor decide if you are eligible to take part in this study. You will answer questions about your diagnosis, the medication you are taking, and the symptoms you are having (for example, pain, fatigue, nausea, appetite problems, sleep problems, depression, and your overall feeling of well-being). Blood (about 1 tablespoon) will be drawn to measure protein levels. The blood work for protein levels and iron are screening tests and done at baseline to see if you have too little iron in your blood. Blood will be drawn to test hemoglobin levels (about 1 tablespoon). It will take about 30 minutes to complete all the screening tests.

If you are found to be eligible for this study, you will be randomly assigned (as in the toss of a coin) to receive either dexamethasone or a placebo by mouth in the morning and at night with food every day for 14 days. A placebo is a substance that looks like the study drug but which has no active ingredients. You will have an equal chance of being placed in either of the 2 groups. You, the medical staff, and researchers will not know to which group you have been assigned.

Beginning on Day 15 [± 3 days], regardless of if you were assigned to the dexamethasone or placebo group during the first 14 days, you will begin receiving the dexamethasone. On Days 15-21, you will receive dexamethasone 2 times a day. On Days 22-28 you will continue to take dexamethasone 2 times a day, but it will be at a lower dose level.

If you develop intolerable side effects while on this study, the medication will be stopped and you will be removed from the study.

You will be asked to return to the outpatient clinic on Days 8 [± 3 days], 15 [± 3 days] , 22 [± 3 days], and 29 [± 3 days] to answer a questionnaire about your cancer diagnosis, the medication you are taking, and the symptoms you are having (for example, pain, fatigue, nausea, appetite problems, sleep problems, depression, and your overall sense of well-being). The questionnaire will take approximately 30 minutes to complete. Blood (about 1 tablespoon) will be drawn to measure protein levels and to check the iron level in your blood. If you are unable to return to the clinic on days 8, 15, 22, or 29; the assessments will be done by the research nurse by phone; the blood work will not be done.

You will be considered off-study on Day 29 [± 3 days]. All study patients will have a 2 week follow-up on day 43 [± 3 days] after study drug has been discontinued, for safety and toxicity assessments. If you are unable to return to the clinic on day 43, the research nurse will do the safety and toxicity assessment by phone.

This is an investigational study. Dexamethasone has been approved by the FDA and is a commercially available drug. It is FDA approved at this dose level. Its use in this study, for this purpose, is investigational. Dexamethasone will be provided free of charge during this study up to Day 29. It can continue to be prescribed to you by your primary doctor after that time, if needed, but you and/or your insurance provider will then be responsible for the cost of the dexamethasone. About 125 patients will take part in this study. Up to 75 will be enrolled at M. D. Anderson. The other sites participating in this study are Lyndon Baines Johnson [LBJ] breast oncology clinic Houston Texas, and Four Seasons Hospice in Flat Rock, North Carolina.

Optional Procedures: If you agree, extra blood (about 1 tablespoon each time) will be drawn and used to study the effect dexamethasone has on proteins in your blood (called cytokines), white blood cells (called monocytes) and cell receptors for these proteins and how changes in these proteins affect the symptoms you have. This blood will be drawn on Days 8, 15, 22, and 29. If you are unable to return to the clinic the blood work will not be done.

If you agree, you will complete a questionnaire at the beginning of the study and on Day 15. The questionnaire asks questions about sleep quality, including bed time, length of time to fall asleep, and symptoms. It takes about 5 minutes to complete.

You will also be asked to provide a saliva sample to test for cortisol levels at the beginning of the study and on Day 15. You will be given detailed instructions on how to collect the saliva samples.

There will be no cost to you for taking part in the optional procedures.

You do not have to agree to take part in the optional procedures in order to receive treatment on this study.

4. RISKS, SIDE EFFECTS, AND DISCOMFORTS TO PARTICIPANTS

While on this study, you are at risk for the side effects listed in this form. You should discuss these with the study doctor or your regular doctor. The known side effects are listed in this form, but they will vary from person to person. Many side effects go away shortly after the study drug is stopped, but in some cases side effects may be serious, long lasting, and/or permanent and may even cause death.

Dexamethasone Side Effects

It is not known how often the side effects of dexamethasone may occur.

rregular heartbeat slow heartbeat cardiac arrest (sudden stopping of the heart) enlarged heart heart failure swelling high blood pressure tearing of the walls of the heart fainting shock depression unstable emotions euphoria (abnormal feelings of great happiness or well-being) headache increased pressure between the skull and brain (possible headache) difficulty sleeping weakness mood swings nerve inflammation personality changes psychotic disorders seizures dizziness acne skin inflammation hair loss tissue swelling bruising dry skin skin redness lightening and/or darkening of the skin fragile skin excessive/increased hair growth spots under the skin skin rash skin thinning skin tests (such as for TB) may not be accurate	decreased function of the adrenal glands, which could affect the body's ability to control blood pressure and/or react to stress increased hormone production (possible difficulty managing weight and muscle weakness) diabetes abnormal blood sugar test (also known as "pre-diabetes") stunted growth in children high blood sugar (possible diabetes) low blood levels of potassium (possibly due to fluid loss) low levels of nitrogen abnormal hormone production (possible fatigue, difficulty managing weight, and/or problems fighting infection) abnormal breakdown of proteins high blood levels of sodium (possible weakness and/or swelling) bleeding in the digestive system abdominal swelling anal itching increased appetite hole in the stomach and/or intestines, which may cause the contents to leak nausea inflammation of the	changes to the menstrual cycle abnormal sperm development blood clot blocking a blood vessel (possible stroke) blood vessel inflammation (possible fever and/or fatigue) inflammation of a vein caused by blood clot enlarged liver abnormal liver tests (possible liver damage) joint disease and/or pain death of bone tissue broken bones loss of muscle mass muscle disease that causes weakness nervous system disease (possible pain and/or weakness) decreased bone density (possible fractures) tickling/tingling sensation rip in a tendon abnormal fat deposit collapse of spinal bones cataracts (clouding of the lens of the eye) bulging eye increased pressure in the eye (possible loss of vision) high levels of sugar in the urine build-up of fluid in the lungs allergic reaction (possibly severe)

stretch marks hives sweating decrease in carbohydrate tolerance	pancreas (possible abdominal pain) sore in the stomach, small intestine, and/or esophagus weight gain	poor blood supply and death of tissue hiccups infection moon face new occurrence of cancer malignant skin lesions wound healing problems

Questionnaires may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. If you have concerns after completing the questionnaire, you are encouraged to contact your doctor or the study chair.

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

This study may involve unpredictable risks to the participants.

Optional Procedures: You may experience pain, bleeding, and/or bruising from the blood draws. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Questionnaires may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. If you have concerns after completing the questionnaire, you are encouraged to contact your doctor or the study chair.

5. POTENTIAL BENEFITS

Treatment on this study may help to control your symptoms. Future patients may benefit from what is learned from this study. There may be no benefits for you in this study.

Optional Procedures: There are no benefits to you for taking part in the optional procedure. Future patients may benefit from what is learned.

6. ALTERNATE PROCEDURES OR TREATMENTS

You may choose not to take part in this study. You may chose to take dexamethasone outside of this study. You may choose other investigational therapy, if available. You may choose not to have treatment for you symptoms of fatigue, pain, nausea, depression or loss of appetite at all. Refusal to take part in this study will not cause penalty or loss of benefits to which you are otherwise entitled.

Optional Procedures: Treatment with the study drug may be given without taking part in the optional procedures.

I understand that the following statements about this study are true:

7. M. D. Anderson may benefit financially from my participation and/or from what is learned in this study.

8. This study is supported by: American Cancer Society (Mentored Research Scholar Grant).

9. I may ask the study chair any questions I have about this study, including questions about the costs. I may contact the study chair, Dr. Sriram Yennurajalingam, at 713-792-6085. I may also contact the Chair of M. D. Anderson's IRB at 713-792-2933 with any questions that have to do with this study or my rights as a study participant.

10. My participation in this research study is strictly voluntary. I may refuse to take part in this study without any penalty or loss of benefits to which I am otherwise entitled. I may also withdraw from participation in this study at any time without any penalty or loss of benefits. I should first discuss leaving the study with my doctor. If I withdraw from this study, I may still be treated at M. D. Anderson.

11. I understand that the study may be changed or stopped at any time by the study chair, American Cancer Society (Mentored Research Scholar Grant), the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP) (a regulatory agency that oversees research in humans), or the IRB of M. D. Anderson.

12. I will be informed of any new findings that might affect my willingness to continue taking part in the study.

13. M. D. Anderson will take appropriate steps to keep my personal health information private. However, there is no guarantee of absolute privacy. Federal agencies (such as the FDA and the OHRP), American Cancer Society (Mentored Research Scholar Grant), and the IRB of M. D. Anderson might review my record to collect data or to check that the research is being done safely and correctly. In some situations, the FDA could be required to reveal the names of participants.

14. If I suffer injury as a direct result of taking part in this study, M. D. Anderson will provide medical care. However, this medical care will be billed to my insurance provider or me in the ordinary manner. I understand that I will not be reimbursed for expenses or compensated financially by M. D. Anderson or American Cancer Society (Mentored Research Scholar Grant) for this injury. I may also contact the Chair of M. D. Anderson's IRB at 713-792-2933 with questions about study-related injuries.

15. Certain tests, procedures, and/or medications that I may receive as part of this study may be without cost to me because they are for research purposes only. However, my insurance provider or I may be financially responsible for the cost of supportive care and treatment of any complications resulting from the research tests, procedures, and/or medications, including hospitalization, nausea, vomiting, low blood cell counts, and dehydration. Standard medical care that I receive under this research study will be billed to my insurance provider and/or me in the ordinary manner. I should learn before taking part in this study which parts of the research-related care will be provided without charge, which costs my insurance provider will pay for, and which costs will be my responsibility. I may ask to speak with a financial counselor about the costs of this study.

16. I understand that there are no plans to compensate me for any patents or discoveries that may result from my participation in this research. I will receive no compensation for taking part in this study.

Authorization for Use and Disclosure of Protected Health Information:

A. During the course of this study, the research team at M. D. Anderson will be collecting information about you. This information may include your medical history, study schedule, and the results of any of your tests, therapies, and/or procedures. The purpose of collecting and

sharing this information is to learn about how the study procedures may affect the disease and any study-related side effects. Your doctor and the research team may share your study information with the parties named in Section E below.

B. If you refuse to provide your authorization to disclose your protected health information, you will not be able to participate in this research study.

C. Your protected health information will be protected according to state and federal law. However, there is no guarantee that your information will remain confidential, and it may be re-disclosed at some point.

D. All identifying information such as your name and address will be kept private. This information may be kept at M. D. Anderson forever. You will be assigned a code number so that your name will not be used. The research team at M. D. Anderson will be able to link the code number to your name. In some instances, in order to ensure the scientific value of the study, the parties named in Section E below will be able to view your study record but will not be permitted to copy any identifying information contained in your record.

E. Your information may be shared with the following parties:

American Cancer Society (Mentored Research Scholar Grant)
The FDA
The OHRP
The IRB of M. D. Anderson
Officials of M. D. Anderson
Clinical study monitors who verify the accuracy of the information
Individuals with medical backgrounds who determine the effect that the study procedures may have on the disease
Individuals who put all the study information together in report form

F. You have the right to see and reproduce your records related to the research study, and ask for corrections, for as long as this information is held by the study chair and/or M. D. Anderson. However, in some studies, in order to ensure the scientific value of the study, participants are not able to view or reproduce their study records until the research has been completed with all participants in the study. If possible for this study, your doctor will be able to discuss your clinical test results with you.

G. There is no expiration date for the use of your protected health information. You may withdraw your authorization to share your protected health information at any time in writing. Instructions on how to do this can be found in the M. D. Anderson Notice of Privacy Practices (NPP). You may contact the IRB Staff at 713-792-2933 with questions about how to find the NPP. If you withdraw your authorization, you will be removed from the study and the study chair and staff will no longer use or disclose your protected health information in connection with this study, unless the study chair or staff needs to use or disclose some of your research-related protected health information to preserve the scientific value of the study. The parties listed in Section E above may use any study data that were collected before you canceled your authorization.

CONSENT/PERMISSION/AUTHORIZATION
FOR TREATMENT AND OPTIONAL PROCEDURES

(Mark choice(s) with an "X")

I elect to ____ or not to ____ extra blood to be drawn as an optional procedure.
Participant's Initials _____

I elect to ____ or not to ____ complete questionnaires as an optional procedure.
Participant's Initials _____

I elect to ____ or not to ____ allow saliva to be collected as an optional procedure.
Participant's Initials _____

Having read and understood the above and having had the chance to ask questions about this study, think about the study, and talk with others as needed, I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I have been given a signed copy of this consent document.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS
SIGNATURE OF PARTICIPANT

DATE

I was present during the explanation of the research to be performed under Protocol **2005-0816**.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS
SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS
SIGNATURE OF PERSON RESPONSIBLE & RELATIONSHIP

DATE

I have discussed this clinical research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF STUDY CHAIR OR PERSON OBTAINING CONSENT DATE

Translator

I have translated the above informed consent as written (without additions or subtractions)
into _____ and assisted the people obtaining/providing
(Name of Language)
consent by translating all questions and responses during the consent process for this participant.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

NAME OF TRANSLATOR SIGNATURE OF TRANSLATOR DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line.)

Appendix F:

Treatment Plan and Standard operating procedure:

This is a prospective, randomized double blind, placebo controlled study comparing the effect of dexamethasone versus placebo. We will randomize 125 eligible patients to receive either dexamethasone 4 mg orally two times a day for 14 days or matching placebo. During the study period, patients will be assessed for the intensity of fatigue, other symptoms and toxicities. Patients will also be assessed by the research nurses for any signs and symptoms of infection while on the study drug. Patients will undergo laboratory tests to measure cytokines.

A physician will do a physical exam on the patient on day 0, 15, and Day 29; If patient is unable to return to clinic on Day 8, 15, 22, or 29 the assessments will be done by the research nurse by phone. Laboratory correlates including cytokine levels- IL-1, IL-6, IL-17 TNF-alpha, IL-10, IL-8, and corresponding receptor levels, will be performed at baseline, Day 15 [± 3 days], and Day 29 [± 3 days. Patients will also be assessed by the research nurses for any signs and symptoms of infection while on the study drug.

All study patients will be asked to return to the clinic for follow-up assessments 2 weeks after the study medication is discontinued (day 43 ± 3 days) for a safety and toxicity assessment. If the patient is unable to return to the clinic on day 43, the safety and toxicity assessment will be done by the research nurse by telephone

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