Proposal To: American Cancer Society *Mentored Research Scholar Grant*
Title (Applicant): ***Effect of Dexamethasone on symptom distress in patients with advanced cancer (Yennurajalingam, Sriram)***

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Title (Applicant): **Effect of Dexamethasone on symptom distress in patients with advanced cancer (Yennurajalingam, Sriram)**

**Project Title** Effect of Dexamethasone on symptom distress in patients with advanced cancer

**Is this proposal in response to a Request for Application (RFA)?** No

**RFA Title:** N/A

**Total Amount Requested:**

**Start Date:**

**End Date:**

**Is this proposal for a new grant or renewal of an existing grant?** New

**Proposal Type**

**ACS Grant#:** N/A.

**Have you submitted this proposal to ACS for funding consideration before?** No

**Prior application number:** N/A.

**First or second resubmission?** If this application is a resubmission, please select if this is your first or second resubmission.

Title: **Effect of dexamethasone on symptom distress in patients with advanced cancer(66 Characters)**

**Project Abstracts & Coding**

**Please provide a General Audience Summary below (< 3,000 characters. Text only. No special characters or formatting. See instructions for details.).**
***Attach the Technical Abstract as a file at the bottom of this page.***

**8.General Audience Summary** Most patients with advanced cancer develop devastating physical and psychosocial symptoms. These symptoms decrease the quality of life of patients and produce severe distress in their families. At present there are limited treatment options to treat these symptoms. Corticosteroids such as Dexamethasone have been widely used in the treatment of symptoms such as fatigue, nausea, anorexia and pain in advanced cancer patients.

Despite widespread use of steroid therapy in cancer symptom management, the data is still inadequate to draw definitive conclusions of the efficacy of these compounds in the management of pain and other symptoms. Previous studies by our group and other investigators on steroids suggested beneficial effects of steroids on these symptoms. But

the studies were done using not validated assessment tools, different types of steroids, administration routes and dosages. Steroids have potentially severe side effects, especially on prolonged use including immunosuppression, osteoporosis, Cushing's syndrome, myopathy, and hyperglycemia. Some of these effects can be particularly serious in patients with advanced cancer. Therefore it is important to better determine the symptomatic effects relative to the potential side effects of these drugs. None of studies described the underlying mechanism of action of steroids on symptoms.
In recent years, it has become evident that many cytokines have powerful effects on the brain. 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 insight into the central effects of these agents. Sickness behavior is typically associated with behavioral changes seen in humans and laboratory animals suffering from microbial infections and includes symptoms of cognitive dysfunction, anxiety, psychomotor slowing, fatigue, anorexia, sleep alterations and increased sensitivity to pain. Relevant to their mediation by cytokines, symptoms of sickness behavior can be reliably reproduced in both laboratory animals and humans by administration of each of the cytokines that induce the pro-inflammatory cytokine cascade (TNF-α, IL-1, IL-6). The cytokines and pro inflammatory mediators are elevated in advanced cancer patients, are associated with these symptoms. Dexamethasone and other steroids could potentially decrease the symptoms specifically, fatigue, nausea, anorexia and pain by decreasing these cytokines and inflammatory substances.
At present, the association between the effects of dexamethasone on symptoms and its effects in decreasing cytokines and inflammatory substances has not been established using validated assessment instruments and laboratory correlates in a randomized controlled trial. Our study will be the first to provide an association. By linking symptomatic response to dexamethasone with the circulating cytokines we will be able to better establish the role of cytokines in the frequency and severity of symptoms. The finding in the study will help in development of cytokine specific suppressive therapies that could be used to prevent and treat these troubling symptoms.

**Selected Research Areas**
Cachexia
Clinical Practice
Immunomodulation
Interleukins
Supportive Care of Cancer Patients
Tumor Necrosis Factor

**Please select two priority areas that are applicable to this project. Then provide a % weighting indicating the relative emphasis of the project for all selected priority areas. Please refer to the ACS Instructions appendix with regard to the common scientific outline terms which are requested below.**

| Selected Priority Areas | % of Project |
|---|---|
| 6.6-End of Life Care | 0 |

**Please select any organ site applicable to this project. For each selection, provide a relative weighting (total must equal 100% or 0%).**

| Selected Organ Sites | % of Project |
|---|---|
| Brain | 0 |

**Project Abstracts & Coding**

**10.STRUCTURED TECHNICAL ABSTRACT**

Name of Applicant: Sriram Yennurajalingam

1. Title of Project: Effect of Dexamethasone on symptom distress in patients with advanced cancer: a randomized controlled trial vs. placebo.

In the 7 x 7-inch space below, summarize concisely your proposed research, outlining background, objective/hypothesis, specific aims, study design, and relevance to the cancer problem. You will prepare the abstract as a separate file when you electronically submit your application. Refer to Application Instructions. If the application is funded, this Abstract will become public information.

## 10.1 BACKGROUND

Approximately 50% of patients diagnosed with cancer die of progressive disease. Patients with advanced cancer experience clusters of physical and psychosocial symptoms including pain, fatigue, nausea, anorexia/cachexia, depression, and sleep disorders [Walsh D, et al, 2000, Paice, 2004; Dodd, et al., 2001; Trask, et al., 2004; Cleeland, 2002]. The prevalence rates of the many different symptoms reported by advanced cancer patients vary as follows: pain 41%-76%, depression 33%-40%, anxiety 57% - 68%, nausea 24%-90%, constipation 65%, sedation/confusion 46%-60%, dyspnea 12%-58%, anorexia 85% and Fatigue 90%[Walsh D, et al., Bruera et al., 2004]. In cancer patients, symptom expression is a multidimensional construct that results from different mechanisms of production and brain perception. There is a complex interaction between the tumor and the host that depends mostly on the tumor mass, the tumor function, the immune status of the host, co-morbidities, and the type of anti-neoplastic treatments being given. It has been noted that somatic nerves deliver afferent information related to symptoms such as pain. The cytokines can influence the stimulation of such afferent nerves at the periphery and some of the central synaptic activity at the dorsal horn and in the brain cortex [Cleeland et al., 2003]. Visceral nerves deliver information regarding symptoms such as dyspnea, nausea, and anorexia and these nerves are also under the influence of cytokines both centrally and peripherally [Cleeland et al., 2003]. Tumor by-products can produce abnormalities that are linked with cancer cachexia [Argiles et al., 2003]. The relationship between tumor by-products and host response has not been completely established. Finally, circulating cytokines and inflammatory proteins have been thought to be directly associated with pain, and cognitive impairment [Lee et al., 2004; Cleeland et al., 2003], depression [O'Brien et al., 2004], fatigue [Kurzrock 2001], cachexia [Bruera 1999], and sleep disorder [Haack et al., 2004].

These symptoms decrease the quality of life of patients. At present there are limited treatment options to treat these symptoms clusters. Corticosteroids such as Dexamethasone have been widely used in treatment of symptoms fatigue, nausea, anorexia, and pain in advanced cancer patients. Despite widespread use of steroid therapy in cancer symptom management, the data is inadequate to draw definitive conclusions about the efficacy of these compounds in the management of pain and other symptoms. Previous studies by our group and other investigators on steroids[Bruera and Roca et al 1985; Tannock I, etal 1996; Kim JH, Fainsinger et al., 1994; A.B. Ettinger et al 1988; T. Popiela, et al, 1989; Della Cuna, et al, 1989; Twycross, 1992; Mercadante, et al 2001; Vecht ChJ, et al 1989; Moertel C, et al., 1974; Stiefel FC, Breitbart WS, et al, 1989]. suggested beneficial effects of steroids on these symptoms in advanced cancer. But the studies were done using assessment tools that were not validated; various different steroids, routes of administration and dosages were used. There was no attempt to understand the pathophysiology using laboratory correlates. The role steroids on cancer related fatigue, pain, appetite and nausea (which are the most common symptoms in advanced cancer), their effects on cytokines need to be defined through randomized controlled studies using updated and validated and laboratory correlates.

**10.2 Objective/ Hypothesis**:

We hypothesize that dexamethasone decreases the intensity of symptoms namely Fatigue, nausea, anorexia and pain that occur frequently in advanced cancer and one of the mechanisms it exerts such effects by decreasing a cytokines levels (namely IL-1, IL-6, TNF-$\alpha$, IL-10, IL-8) that mediate these symptoms.

10.3 **Specific Aims:**

We intend to test the effect of dexamethasone on symptoms in advanced cancer patients by pursuing the following three specific aims:

- Primary objective: To determine the effect of Dexamethasone on the intensity of Fatigue
- Secondary objective-1: To determine the effect of Dexamethasone on the intensity of Pain, anorexia and nausea.
- Secondary objective–2: To determine the changes in cytokines (IL-1, IL-6, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels) and C-reactive protein before and after treatment with dexamethasone.
- Secondary objective-3: To determine association of cytokines (IL-1, IL-6, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels) and C-reactive protein and Fatigue, Pain, Anorexia and nausea.
- Secondary objective – 4: To collect pilot data on the quality of sleep and cortisol levels in ten subjects

**10.4 Study Design**

We will conduct a prospective, randomized, double blind, placebo controlled study comparing Dexamethasone 4mg orally two times per day for 14 days versus placebo. 100 Eligible patients who agree to participate in the study and provide written informed consent will be randomized to either group A, in which patients will receive Dexamethasone orally, 4mg two times a day for 14 days; or group B, in which patients will receive placebo orally, two times a day for 14 days. On day 15, all patients will be receive 4mg of dexamethasone twice a day on a open label basis till Day 21,From Day 22 to Day28 the dose of dexamethasone is to be tapered to 2mg orally twice a day. Subsequently patients would be off study with dose tapered to the minimum tolerated dose. 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 $\pm$ 3 days) for a safety and toxicity assessment. The reason to have open label design after Day15 is to observe the descriptive trends.

Exam (including history including FACIT-F, FAACT, HADS, ESAS, BPI, physical exam and toxicity assessment will be done day 0(baseline), Day 8 [$\pm$3], Day 15[$\pm$3], Day 22[$\pm$3], Day 29[$\pm$3]. GSE on days 8 [$\pm$3], 22[$\pm$3] and 29[$\pm$3]. Patients will also be assessed by the research nurses for any signs and symptoms of infection while on the study drug. Laboratory correlates including cytokine levels- IL-1, IL-6, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels, complete blood counts, chemistry (electrolytes), C-reactive protein on day 0(baseline), Day 8, Day 15, Day 22, Day 29. The ESAS and Toxicity evaluation on Day 4 would be done through the phone.

A subset of ten patients will be asked to complete the Pittsburg Sleep Quality Index at baseline and Day 15 [+ 3]. These patients will also collect saliva cortisol specimens at baseline and Day 15 [+ 3]. We will select the subset of 10 patients sequentially. Every patient will be approached regarding the optional procedure of participating in the quality of sleep questionnaires and the cortisol levels, We will collect the pilot data on the first 10 patients that consent.

**10.5 Cancer Relevance**

Approximately 50% of patients diagnosed with cancer die of progressive disease. The overwhelming majority of patients develop devastating physical and psychosocial symptoms. Those symptoms decrease the quality of life of patients. Circulating cytokines and inflammatory proteins have been thought to be directly associated with pain, and cognitive impairment, depression, fatigue, cachexia, and sleep disorder. Steroids decreases the intensity of symptoms namely Fatigue, nausea, anorexia and pain that occur frequently in advanced cancer and one of the mechanisms it exerts such effects by decreasing a cytokines levels that mediate these symptoms. Despite widespread acceptance and frequency of steroid therapy in patients with cancer symptom management, the data is inadequate to draw definitive conclusions about the efficacy of these compounds in the management of pain and other symptoms. The role steroids on cancer related fatigue, pain, appetite and nausea (which are common symptoms in advanced cancer), their effects on cytokines need to be defined through randomized controlled studies using updated and validated Symptom assessment tools and laboratory correlates (which were lacking in the previous studies on corticosteroids for symptoms). Our findings will also allow investigators 1) To effectively treat the

symptoms clusters in advanced cancer patients and improve their quality of life. 2) Establish Cause and effect relationship between symptoms and cytokines. 3) To establish the use of dexamethasone for symptom control in advance cancer patients through randomized controlled studies using updated and validated Symptom assessment tools and laboratory correlates 4) Development of cytokine specific suppressive therapies that could be used to prevent and treat these troubling symptoms.

**Assurances & Certifications**

**Human Subjects**

**Does the proposed project involve Human Subjects?** Yes

**If Yes, Status of IRB Approval** Pending

**Approved or Pending Date**

**Human Subjects Assurance Number**
FWA363
*This assurance number cannot be entered on this screen – it will appear only if properly entered in the institution profile (for the institution you selected in the institution section of the proposal). If no assurance number appears here, please contact your institution's grants and contacts office to have them add the assurance numbers to the institution profile. If you need assistance, contact proposalCENTRAL customer support.*

**Does the proposed project involve Vertebrate Animals?** No

**If Yes, status of IACUC approval**

**Approved or Pending Date**

**Animal Welfare Assurance Number**
A-3343-1
*This assurance number cannot be entered on this screen – it will appear only if properly entered in the institution profile (for the institution you selected in the institution section of the proposal). If no assurance number appears here, please contact your institution's grants and contacts office to have them add the assurance numbers to the institution profile. If you need assistance, contact proposalCENTRAL customer support.*

**Does the Proposed project involve Recombinant DNA?** No

**If Yes Status of Approval**

**Approved or Pending Date**

**Are hazardous materials used or produced in the project?** No

**If yes Explain:**

**Animal species**

**If vertebrate animals will be used, please list all species, separated by commas.**

**Assurances & Certifications**
**CONTENTS**

# Cover Pages – (Signature Page, Contact Page, Assurances and Certification, General Audience Summary)

# Structured Technical Abstract

**PART I**



**PART II**

**BUDGET**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| A. Personnel<br>*(indicate percent effort, salary, and names of personnel)*<br>Percent of effort:<br>S Yennurajalingam FTE 60%<br>Research nurse FTE 40%<br>Data Manager FTE 20% | | | | | |
| Fringe Benefits Total | | | | | |
| *Category Total* | | | | | |
| B. Permanent Equipment *(Itemize)* | | | | | |
| *Category Total* | | | | | |
| C. Supplies *(Group into major categories)*<br>Drug<br>HADS forms (100 x 4 x $ 1.00)<br>Cytokine assay<br>C- Reactive protein | | | | | |
| *Category Total* | | | | | |
| D. Travel (Domestic only)<br>1,500 x 2 for presentation of 2 papers that are planned to be written based on the study | | | | | |
| *Category Total* | | | | | |
| E. Miscellaneous<br>*(List specific amounts for each item)* | | | | | |
| *Category Total* | | | | | |
| F. Subcontracts *(Categorize on continuation page)* | | | | | |
| *Category Total* | | | | | |
| **Total Direct Costs** | | | | | |
| G. Indirect Costs:___%) *(Excluding permanent equipment)*<br>*Total Indirect Costs* | | | | | |
| **Total Annual Costs** | | | | | |
| **Total Amount Requested**<br>*(Sum of all years including indirect costs; transfer this amount to the budget section of the on-line form)* | | | | | |

**JUSTIFICATION OF BUDGET**

Justify all items of equipment costing over $500, and the need for personnel, supplies, travel, and other items.

**PERSONNEL**

- Eduardo Bruera, M.D., Co-Investigator and Mentor (10% FTE) Dr. Bruera is a medical oncologist who specializes in palliative care. Dr. Bruera is the F. T. McGraw Chair in the Treatment of Cancer and heads the Department Palliative Care and Rehabilitation Medicine. Dr. Bruera has Mentored in design the study and will oversee all aspects of the execution and analysis of the protocol.
- Saroj Vadhan-Raj, Co-investigator and additional Mentor (5% FTE) Dr. Vadhan is a medical oncologist who is a section chief of Medical Supportive Care in the Department of Palliative Care and Rehabilitation Medicine at UTMDACC. Dr. Vahdan collaborates with us in research currently conducted at UTMDACC. She will be responsible, primarily, for conducting and evaluating cytokine measuring. She has mentored and helped design and write this application, will collaborate in the interpretation of the results and the preparation of manuscripts resulting from this study.
- Sriram Yennurajalingam, MD, principal Investigator (60% FTE) Dr. Yennurajalingam is an Symptom control and Palliative care specialist who completed his doctoral fellowship in the Department of Palliative Care and Rehabilitation Medicine at M. D. Anderson Cancer Center, and became an assistant professor and attending physician in the department in 2004. He has great interest in the relationship between symptom clusters and cytokine production and symptom management.

  Dr Yennurajalingam has designed the study and will oversee all aspects of the execution and analysis of the protocol. He will be responsible for the presentation of the study in peer-reviewed meetings and for the publication of the final manuscript.

- Lynn Palmer, Ph.D., Co-investigator and additional mentor (20% FTE) Dr. Palmer is Associate Professor of Biostatistics in the Department of Palliative Care and Rehabilitation Medicine and in the Department of Biostatistics. Dr. Palmer has 24 years experience as a biostatistician, has designed and analyzed a large number of clinical trials and other studies related to the treatment of cancer, and has authored or co-authored numerous publications, including many manuscripts in palliative care. Dr. Palmer will contribute to the design of the study and be responsible for all bio statistical aspects of the study. She will analyze and interpret the data from the clinical trial and assist in manuscript preparation.

- Jie Willey, R.N., MSN, Research Nurse Manager (30% FTE) Ms. Willey is a research nurse manager in the Department of Palliative Care & Rehabilitation Medicine. She has extensive clinical, administrative, and supervisory experience in research development, implementation and administration in the area of breast cancer and symptom management. She will coordinate this research study by supervising the research staff, reassuring patient accrual, study implementation, and data collection and monitoring. She will maintain protocols according to institutional guidelines, monitor study progress, and prepare progress reports for the institution and funding source.

- Mary Abanto, RN BSN, (40% FTE) Ms. Abanto is a research nurse in the Department of Palliative Care & Rehabilitation Medicine. She will be responsible for patient screening and recruiting. She will administrate the assessment measures during clinic visit, and will ensure the blood collection for cytokine levels. She will maintain contact with the patients to ensure all study related data are accurately collected.

- Karen Zhang, MS, Data Manager, (20% FTE) Ms. Zhang will be responsible for all aspects of data management of the project. She will develop databases for the data collected. She will perform data entry and manage the databases. She will assist the statistician in data analyses.

**NON-PERSONNEL BUDGET ITEMS**

Supplies
Drug
HADS
CYTOKINE ASSAY

**BIOGRAPHICAL INFORMATION OF APPLICANT**
*(Do not exceed two pages for total biographical information.)*

Last name, First name YENNURAJALINGAM, SRIRAM

## Education

| Degree/Year Conferred | Institution/Location | Field of Study |
|---|---|---|
| M.B.B.S. (Bachelor of Medicine and Bachelor of Surgery) | Osmania Medical College, University of Health Sciences, Hyderabad, India, 1995 | Medicine |

## Training

| Title | Mentor | Institution | Dates |
|---|---|---|---|
| Fellowship in Symptom control and Palliative Care | Eduardo Bruera MD | UT M. D. Anderson Cancer Center, Houston, TX, 07/2003-06/2004 | 2003 – date |
| Fellowship in Geriatrics | Dharmarajan MD | University Hospital of New York Medical College, Our lady Mercy Medical Center, Bronx, NY | 07/2002 – 06/2003 |
| Residency in Internal Medicine | Ida Ashley MD | Mount Sinai Services (Affiliated to Mount Sinai School of Medicine), Queens Hospital Center, Queens, NY | 07/1999-06/2002 |

## Appointments

| Title | Institution | Dates |
|---|---|---|
| | Department of Palliative Care and Rehabilitation Medicine, The University of Texas M.D. Anderson Cancer Center, | 7/2004 – 8/2004 |

| | | |
|---|---|---|
| Temporary Director<br><br>Assistant Professor of Medicine | Houston, Texas<br><br>Department of Palliative Care and Rehabilitation Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, Texas | 9/2004- to date |

| Justification of Eligibility (if appropriate) |
|---|
| Junior Faculty in 1st year of appointment. |
| **Eligibility Status** |
| Year last degree conferred: MBBS<br>Year of first independent position: 2004 * enter date in appropriate box on Title page |

**BIOGRAPHICAL INFORMATION OF APPLICANT**

**CERTIFICATIONS:**

ECFMG Certification (Steps I, II & III passed), 1995-indefinite

Internal Medicine Board Certified, 08/2002.

Geriatrics Board Certified, 11/2003.

Palliative Care Board Certified, 11/2004

**PROFESSIONAL ACTIVITIES:**

Rotating Intern, Osmania General Hospital and affiliates, in Hyderabad, India, 1994-1995
Internship consisting of practical experience in Medicine & Dermatology (3 months), General Surgery, Ophthalmology & Orthopedic Surgery (3 months), Gynecology & Obstetrics (2 months), Pediatrics (1 month), Infectious Diseases (1 month), Emergency Medicine (1 month), Social & Preventive Medicine (1 month).

Senior House Officer, Department of General Medicine and Psychiatry, Osmania General Hospital and affiliates, Hyderabad, India, 1995-1997

Voluntary Clinical Externship, Ambulatory Care (ER), VA Medical Center,
Dallas, TX, 1997-1998

Voluntary Clinical Externship, Internal Medicine, Conemaugh Memorial Hospital, Johnstown, PA and Queens Hospital Center, Queens, NY, 1998-1999
Resident, Internal Medicine, Mount Sinai Services (Affiliated to Mount Sinai School of Medicine), Queens Hospital Center, Queens, NY, 07/1999-06-2002

Fellowship, Geriatrics at University Hospital of New York Medical College, Our lady Mercy Medical Center, Bronx, NY, 07/2002-06/2003

Fellowship, Symptom Control and Palliative Care, The University of Texas M. D. Anderson Cancer Center, TX, 06/2003-07-2004

**HONORS AND AWARDS**
National Merit Scholarship, 1986

**PUBLICATIONS** *(if partial list is given, indicate total number of publications)*:

Sharma U, Mojab H, **Yennurajalingam S**, Chokhavatia S, Opran A. Systemic vasculitis presenting with abdominal pain and metabolic acidosis. American Journal of Gastroenterology 2002; 97 (9): S164-S164

Noel D, **Yennurajalingam S**, Reich D, Sachmechi I. Four-Year Retrospective Analysis Examining Adherence to Five of The American Diabetes Association (ADA) Guidelines for Diabetic Care. The Mount Sinai J of Med. 2004:212

**Yennurajalingam S**, Peuckmann V, Bruera E. Recent Developments in Cancer Pain Assessment and Management. Supportive Cancer Therapy 2004; 1(2): 97-110.
**Yennurajalingam S**, Braiteh, F, Bruera E. Pain and Terminal Delirium Research in the Elderly. Clin Geriatr Med 2005; 21:93-119.

| **BIOGRAPHICAL INFORMATION OF KEY PERSONNEL**<br>*(Do not exceed two pages per person for total biographical information.)* | | |
|---|---|---|
| Last name, first name | | |
| **Education** | | |
| Degree/Year Conferred | Institution/Location | Field of Study |
| | | |
| **Appointments** | | |
| Title | Institution | Dates |

| | | |
|---|---|---|
| Publications<br><br>*(If partial list is given, indicate total number of publications.)* | | |

**OTHER SUPPORT**
(Current and pending)

Provide details of: Current and Pending support for all professionals listed in the Budget, and Institutional Support to the applicant, as described in the INSTRUCTIONS FOR APPLICATION FOR A MENTORED RESEARCH SCHOLAR GRANT.

Current Support: none

Pending: none.

**PLANS FOR WORK UNDER THE GRANT:**
RESEARCH PLAN (Sections A-E):

### A. Experience

I am an Assistant professor of Medicine in Symptom control and Palliative care in the Department of Palliative care and rehabilitation Medicine at M.D. Anderson Cancer Center. I currently devote 90% of patient care and 10% in clinical research. Receipt of this award would enable me to increase my research effort to 60%. I would use this opportunity to understand the pathophysiological process of symptoms that are severe and prevalent in advanced cancer patient.

After graduation Osmania Medical College, India in 1995, my career goal was to alleviate the suffering in most vulnerable elderly patients cancer patients. Hence I pursued further studies in Internal Medicine in Mount Sinai, Queens Hospital center and Geriatrics in New York Medical College. Subsequently I underwent Training in symptom control and palliative care fellowship in M.D Anderson Cancer Center where I had an opportunity to work with many well-known Medical oncologists and symptom control/ Palliative care specialists. During my training in fellowship I learned clinical skills and medical management of symptoms in wide variety of malignancies. In additions to the clinical experience my training included teaching to the residents and visitors and presentations. My Research experience include clinical research in the form of retrospective studies on symptom management by symptom control and palliative care consult team, role of family conference in enhancing end of life care in advanced cancer patient and review of challenges involved in the management of cancer pain. I am also involved as a co-investigator for the study of thalidomide. In addition I have been a collaborator in various studies which include A Multicenter, Randomized, Double-Blind, Placebo-controlled Study of Darbepoetin Alfa for the Treatment of Anemia of Cancer, 2004-0255, PI Vadhan, Saroj, M.D., 2005, A Double-Blind Placebo Controlled Study of Methylnaltrexone (MNTX) for the Relief of Constipation due to Chronic Opioid Therapy in Patients with Advanced Cancer, DM03-0026, PI Zhukovsky, Donna S., M.D., 2005, The Effect of Methadone on QTc Intervals, 2005-015, PI Reddy, Suresh, M.D., 2005,

Validation study the revised Edmonton symptom assessment scale, 2005. In addition I am actively involved in publication of articles in peer-reviewed journals and Oncology and palliative care textbooks.

**Career goals**

My immediate career Objective is to develop the knowledge and skills necessary to compete for independent research support

My specific interest is the role of cytokines and other inflammatory substances in the causation of symptoms. The short-term goal is to establish the use of dexamethasone for symptom control in advance cancer patients through randomized controlled studies using updated and validated Symptom assessment tools and laboratory correlates. The long-term goal is to the goals to develop strategies based on pathophysiology (by using laboratory correlates) to effectively treat the symptoms clusters in advanced cancer patients and improve their quality of life. This includes development of cytokine specific suppressive therapies that could be used to prevent and treat these troubling symptoms.

With a strong clinical background and being motivated, focused and perseverant, I am confident to make significant difference in reducing the symptoms in cancer patients and thereby their quality of life. This award will enable me to receive high quality, multidisciplinary didactic training so that I will be well grounded the principles and techniques for the research on human subjects. In addition, it would release me from more routine aspects of patient care responsibilities so that I can focus on investigator-initiated research.

With my strong background in patient care and further training in patient-oriented research, I will be better positioned to develop therapies, specifically symptom clusters in cancer patients.

**Career Development Activities during Award Period**

To achieve the goal of being an independent clinical investigator, I propose a comprehensive didactic training program with focus on biostatistics and clinical trial methodology. The major portion of my didactic training program is to obtain Master of Sciences (MS) in Clinical Research Program at UT Health Science Center at Houston Medical School (MD Anderson is part of UT Health Science Center). This MS degree program is designed as a focused and flexible program to train clinical investigators in designing and conducting patient-oriented research of exemplary. The courses are concentrated on Wednesday afternoons. The degree can be completed in minimum of 2 years. The MS Clinical Research Curriculum Topics include (Please see attached appendix 3 for the Master of Science in Clinical Research Degree Program Catalog Addendum):

1. Clinical Epidemiology (14 weeks)
2. Clinical Trials (13 weeks)
3. Seminars in Clinical Research (13 weeks)
4. Use of Computers in Clinical Research (lab course, flexible schedule)
5. Scientific Writing (8 weeks)
6. Biostatistics for Clinical Research (15 weeks)
7. Literature Appraisal (8 weeks)
8. Ethical Aspects of Clinical Research (5 weeks)
9. Introduction to Translational Research (7 weeks)
10. Clinical Research Design Workshop (12 weeks)
11. Evaluating Costs and Benefits in Clinical Research (Elective)
12. Using Research to inform Health Care Policy and Practice (Elective)
13. Molecular and Cellular Approaches to Human Genetics (Elective)

14. Genetics and Human Disease (Elective)

Advanced Course for Master's Program (required)

- Advanced Epidemiology (Wednesday afternoon)
  This course covers the analysis of complex observational studies with emphasis on the identification of interaction and control of confounding variables. Other topics include the use of matching, selection of appropriate control groups, and identification of potential sources of bias. A problem-based approach is used in which students are asked to solve design and analysis problems using existing data sets.

- Advanced Biostatistics for Clinical Investigators (Wednesday afternoon)
  This course will focus on the mechanics of applying biostatistical techniques in a research setting. Emphasis will be placed on assumption testing and techniques of model fitting. Students will be expected to critically evaluate, develop, and execute analysis plans using descriptive analysis and regression techniques.

The following table is a sample two-year completion schedule for MS in Clinical Research Program

| Sample Two-Year Completion Schedule<br><br>Patient-Based Clinical Research Track | | | | |
|---|---|---|---|---|
| Academic Year | Course Type | Fall | Spring | Summer |
| 2006-2007 | CRCA<br><br>(Wed: 5:00-6:30) | Biostatistics for Clinical Investigators | Literature appraisal<br>Ethical Aspects of Clinical Research<br>Introduction to Translational Research | Seminars in Clinical Research<br>Use of Computers in Clinical Research (flexible schedule) |
| | Advanced<br><br>(Wed: 1:00-4:30) | Evaluating Costs and Benefits in Clinical Research | Advanced Biostatistics | |
| | Other | Practicum | Practicum | Practicum |
| 2007-2008 | CRCA<br><br>(Wed: 5:00-6:30) | Clinical Epidemiology<br>Clinical Trials | Clinical Trials (cont)<br>Clinical Research Design Workshop | Scientific Writing |

| | | | | |
|---|---|---|---|---|
| | Advanced<br><br>(Wed: 1:00-4:30) | Using Research to Inform Health Care Policy and Practice | Advanced Epidemiology | |
| | Other | Thesis | Thesis | Thesis |

Besides MS program training, I will participate in a variety of scientific meetings and seminars, including:

- Grand Rounds at the Division of Medicine (Tuesdays) and M. D. Anderson (Fridays): Nationally recognized researchers and investigators from M. D. Anderson are invited to give lectures on cancer research and treatment at both Grand Rounds.

- Multidisciplinary Conferences in Symptom control and Palliative care l Tuesdays, and Thursdays: In each conference, a multidisciplinary team, discusses the complicated and challenging cases and plan for optimal treatment.

- Research Seminars (Thursdays): The Dept. of symptom control and Palliative care has a weekly research seminar.

- Phase I and II Meeting (Wednesdays): This weekly meeting is chaired by Dr. Razelle Kuszrock(Phase I) and Dr. Hagop Kantargen (Phase II). Investigators from the institution discuss progress and opportunities available from NCI-sponsored phase I and II clinical trials. Every month, investigators give presentations about ongoing clinical trials, study design, and progress in relevant research fields.

**B.Specific Aims:**

Previous research has shown that patients with advanced cancer develop clusters of physical and psychosocial symptoms [1-4]. The brain is the ultimate organ where symptoms are perceived [5]. In recent years a number of cytokines and other pro-inflammatory mediators produced by the host in response to the presence of cancer have been associated with a number of these symptoms including pain [5,6], cognitive impairment [5-6], depression [7], fatigue [8], cachexia [9], and sleep disorder [10].

A number of pharmacological interventions have been found to be capable of reducing some of the severe symptoms associated with cancer, AIDS, and other chronic infections where cytokines have been identified as playing a major role [11,12]. Our group [13] and others [14-27] have found that corticosteroids are capable of improving symptoms such as fatigue, anorexia, pain, and anorexia/cachexia in patients with cancer.

Dexamethasone has been found to exert complex effects on a number of major cytokines [28-33]

Our **long-term goal** is to better understand the role of cytokines in the frequency and severity of symptoms. The **objective** of the study is to find association between the effects of dexamethasone on symptoms and its effects in decreasing cytokines and inflammatory substances. We **hypothesize** that dexamethasone decreases the intensity of symptoms namely Fatigue, nausea, anorexia and pain that occur frequently in advanced cancer and one of the mechanisms it exerts such effects by decreasing a cytokines levels (namely IL-1, IL-6, TNF-$\alpha$, IL-10, IL-8) that mediate these symptoms. The **rationale** for the proposed research is despite the prevalence of severe symptom clusters in patients with advanced cancer there has been limited research on treatment of these symptom clusters. Corticosteroids such as Dexamethasone have been widely used in treatment of symptoms fatigue, nausea, anorexia, and pain in advanced cancer patients. Despite widespread use of steroid therapy in cancer symptom management, the data is inadequate to draw definitive conclusions about the efficacy of these compounds in the management of pain and other symptoms. Previous studies by our group and other investigators on steroids suggested beneficial effects of steroids on these symptoms in advanced cancer. But the studies were done using assessment tools that were not validated; various different steroids, routes of administration and dosages were used.

We intend to test the effect of dexamethasone on symptoms in advanced cancer patients by pursuing the following three specific aims:

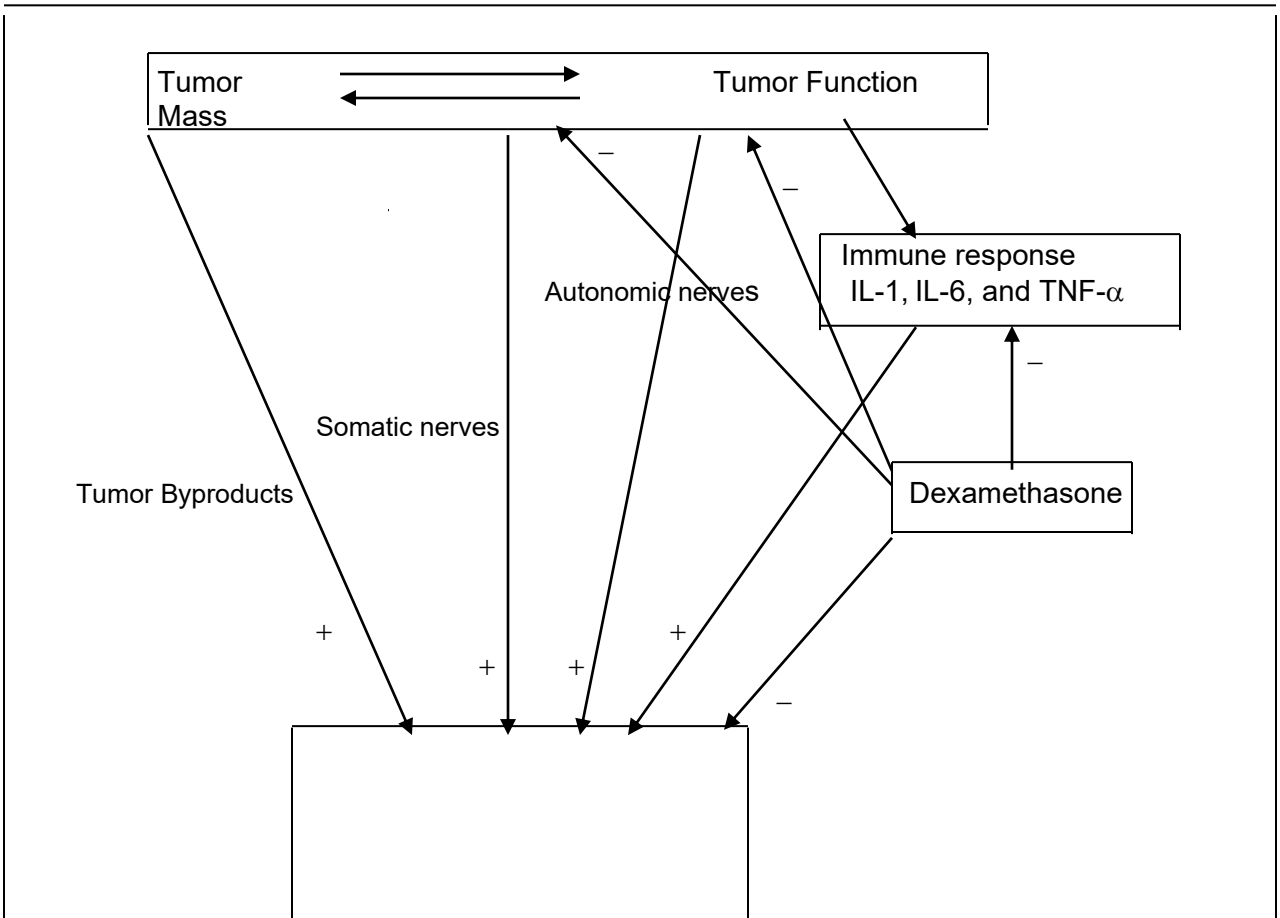
- Primary objective: To determine the effect of Dexamethasone on the intensity of Fatigue
- Secondary objective-1: To determine the effect of Dexamethasone on the intensity of Pain, anorexia and nausea.
- Secondary objective-2: To determine the changes in cytokines (IL-1, IL-6, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels) and C-reactive protein before and after treatment with dexamethasone.
- Secondary objective-3: To determine association of cytokines (IL-1, IL-6, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels) and C-reactive protein and Fatigue, Pain, Anorexia and nausea.

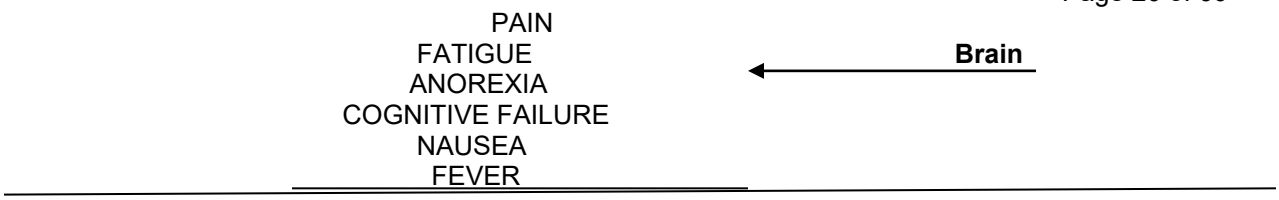
- Secondary objective – 4: To collect pilot data on the quality of sleep and cortisol levels in ten subjects

**C. Background:**

Approximately 50% of patients diagnosed with cancer die of progressive disease. Patients with advanced cancer experience clusters of physical and psychosocial symptoms including pain, fatigue, nausea, anorexia/cachexia, depression, and sleep disorders [1-4,34]. The prevalence rates of the many different symptoms reported by advanced cancer patients vary as follows: pain 41%-76%, depression 33%-40%, anxiety 57% - 68%, nausea 24%-90%, constipation 65%, sedation/confusion 46%-60%, dyspnea 12%-58%, anorexia 85% and Fatigue 90%[34,35]. In cancer patients, symptom expression is a multidimensional construct that results from different mechanisms of production and brain perception. There is a complex interaction between the tumor and the host that depends mostly on the tumor mass, the tumor function, the immune status of the host, co-morbidities.

It has been noted that somatic nerves deliver afferent information related to symptoms such as pain, and cytokines can influence the stimulation of such afferent nerves at the periphery and some of the central synaptic activity at the dorsal horn and in the brain cortex [6]. Visceral nerves deliver information regarding symptoms such as dyspnea, nausea, and anorexia and these nerves are also under the influence of cytokines both centrally and peripherally [6]. Tumor by-products can produce abnormalities that are linked with cancer cachexia [36]. The relationship between tumor by-products and host response has not been completely established. Finally, circulating cytokines and inflammatory proteins have been thought to be directly associated with pain, and cognitive impairment [5,6], depression [7], fatigue [37], cachexia [38], and sleep disorder [10].
Fig. 1






**The Role of Cytokines and Pro-inflammatory Mediators on Symptom Production**

As shown in Figure 1, cytokines have been associated with the presence of the tumor, co-morbidities such as infections, and the effects of cancer treatments including radiation therapy and cytotoxic therapy.
In recent years, it has become evident that many cytokines have powerful effects on the brain. 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 insight into the central effects of these agents [6].

Sickness behavior is typically associated with behavioral changes seen in humans and laboratory animals suffering from microbial infections and includes symptoms of cognitive dysfunction, anxiety, psychomotor slowing, fatigue, anorexia, sleep alterations and increased sensitivity to pain [39]. Relevant to their mediation by cytokines, symptoms of sickness behavior can be reliably reproduced in both laboratory animals and humans by administration of each of the cytokines that induce the pro-inflammatory cytokine cascade (TNF-α to IL-1 to IL-6) [40].

One of the mechanisms cytokines mediate symptoms is through an array of signals through the hypothalamic-pituitary-adrenal axis or circardian axis. Laboratory studies show that administration of IL-6 increases serum glucocorticoid levels through hypothalamic pathways [41]. TGF-$\alpha$ mediates hypothalamic signaling for circardian regulation of motor activity, sleep, and body temperature[42]. Data taken together in the form of cortisol circadian rhythms, symptoms and poor prognosis suggest close relationships[43]. In patients with chronic stress from cancer, altered patterns of cortisol rhythmicity are associated with poor prognosis [41].

*Cytokines and fatigue*
Fatigue is the most common symptom associated with cancer and cancer treatment. Researchers have proposed that one possible explanation for the development of fatigue in cancer patients is the increased secretion of pro inflammatory cytokines in response to both the disease itself and the treatment [8,44]. Fatigue symptoms are multifactorial. It has been reported that pro inflammatory cytokines can act at the level of mood, muscle mass and strength, and metabolic status to induce fatigue [5,8]. Studies in rats and mice showed that increased signs of fatigue when infection and other conditions associated with an increase in pro inflammatory cytokines were present [45,46]. Drugs such as IFN- α, IL-2 and TNF- α have been associated with symptoms such as fatigue, mood changes, sleep disturbance, and cognitive changes [47]. Cytokine associated symptoms including anorexia/cachexia, chronic nausea, fever, depression, pain, and sleep disorders can also contribute to fatigue [48-49]. Previous studies showed that cytokines have been implicated in the pathophysiology of fatigue on the basis of several lines of evidence, including: 1) their increased levels in non-oncologic conditions

characterized by fatigue, such as chronic fatigue syndrome [50-53]; 2) the occurrence of fatigue as a major side effect of cytokines (interleukins, TNF, and interferon) used in the treatment of cancer patients [54-58]; and 3) the up regulation of pro-inflammatory cytokines and their correlation with fatigue in several malignancies [44,59,60) Chemotherapy treatment of cancer results in elevation of cytokines [61]

*Cytokines and pain*

A variety of recent research has uncovered a role for immune-to-brain communication and brain cytokines in aspects of sensory processing. Animal models of hyperalgesia suggested that cytokines might contribute to cancer-related pain [62]. Cytokines such as IL-1 and TNF-α have been associated with aggravation of pain in experimental models [63]. Research has demonstrated that simply attracting immune cells that release pro-inflammatory cytokines in the regions of the nerve produces long-lasting pain enhancement [64], and that blocking IL-1 receptors can reverse ongoing chronic exaggerated pain [65]. In cancer treatments, increased release of cytokines (IL-1, IL-6, IFN-α, TNF-α) was observed in patients receiving cisplatin [66], taxol [67], vincristine [68] and irradiation [69,70], and who showed clinical manifestation of neuropathic pain-like syndromes.

*Cytokines and anorexia, cachexia and chronic nausea*

Cancer anorexia/cachexia syndrome is often observed in patients with advanced stages of cancer. Patients with this wasting syndrome experience diverse symptoms such as progressive bodyweight loss, chronic nausea, fatigue, sleep disorders and a decreased sense of well being [71]. In recent years, cancer cachexia has been recognized as a result of major metabolic disarray because of complex mechanisms involving tumor by-products and host cytokine release, in particular TNF- α, rather than a simple increase in energy consumption by the tumor and starvation by the patient. Cytokines, such as TNF-α, IL-1, IL-6 and IL-8 have been shown to induce anorexia/cachexia by lipolysis and other metabolic effects, and by direct action in the central nervous system (CNS) [72-74]. Researchers measured various specific components of the cytokine-induced anorectic reaction, and found that IL-1β, TNF-α, and IFN-γ messenger RNA were detected in the tumor tissue of anorectic tumor-bearing rats [75]. This suggests that IL-1β and its receptor may play a significant role in this model of cancer-associated anorexia. IL-6 has been revealed as a key mediator of food intake in an experimental sepsis model in mice [Leon et al., 1998]. It is likely that close interrelation among these mediators (IL-1, IL-6, TNF-α and IFN) exists in the hypothalamus, decreasing food intake and leading to cachexia [76].

*Cytokines and cognitive impairment*

The pro-inflammatory cytokines have been considered as immune-to-brain signaling molecules [63]. Interleukin 1 α and β (IL-1 α and β), tumor necrosis factor- α (TNF- α), and IL-6 are key elements signal the brain. A number of observations suggest that immune-to-brain communication and the consequent induction of cytokines might produce cognitive disturbances that include interference with the formation of memories [77,78]. Further evidence from women with breast cancer indicates that the hormone-ablative agent tamoxifen affects several neurotransmitters and cytokines (e.g. IL-1, IL-6, IFN- α, TNF-α) implicated in cognitive functioning [78].

*Cytokines and sleep disorders*

Studies have shown that by crossing the blood-brain barrier and through peripheral autonomic efferent nerves, the peripheral cytokines can communicate and signal the brain to elicit central nervous system manifestation, e.g. sleepiness [79]. In Vgontzas'

study, it was evident that the reduction of sleepiness was found to be associated with decreased IL-6 levels in patients with excessive daytime sleepiness [80]. Other researches have found that the deterioration in the quality and quantity of nighttime sleep is associated with alterations of IL-6 and TNFα [10,80].

*Cytokines and fever*

The mechanism of neoplastic fever is thought to involve inflammatory cytokines such as TNF- α, IL-1, IL-6 that are produced either by host macrophages in response to the tumor or by the tumor itself [Leon et al., 1998]. Cytokines such as IL-1, TNF-α, and IFN, which are released by neoplastic cells (i.e. renal carcinoma, lymphomas, and acute myelogenous and chronic myelogenous leukemia) are pyrogenic [81].

It is remarkable that a relatively small number of cytokines are repeatedly associated with a large number of symptoms in patients with advanced cancer. In particular, IL-1, IL-6, TNF-α, and IFN are most commonly associated with the symptom clusters that are most frequently observed in advanced cancer.

*Cytokines and depression*

Clinical and experimental studies on animals indicate that depression is associated with increased plasma cytokine (IL-1, IL-6 and TNF-α) acute phase protein concentrations and hypothalamic-pituitary-adrenal axia (HPA) activation [7]. Previous studies have suggested that hyper secretion of cytokines in response to stress or to endogenous trigger factors may induce depressive symptoms [77]. The role of cytokines in depression was first considered when IFN resulted in “sickness behavior,” the symptoms of which are similar to those of major depression [7].
Table I shows the main cytokines identified as associated with a number of specific symptoms.

It is remarkable that a relatively small number of cytokines are repeatedly associated with a large number of symptoms in patients with advanced cancer. In particular, TNF, IL-1, IL-6, and interferon are most commonly associated with the symptom clusters that are most frequently observed in advanced cancer.

| Symptoms | Associated Cytokines |
|---|---|
| Fatigue | IL-1, IL-6, IFN-α, TNF-α |
| Anorexia/cachexia | IL-1, IL-6, IFN-α, TNF-α |
| Fever | IL-1, IL-2, IL-6, IL-12, IFN-α, TNF-α |
| Depression | IL-1, IL-6, IFN-α, TNF-α |
| Sleep disorder | IL-6, TNF-α |
| Cognitive impairment | IL-1, IFN- α |
| Pain | IL-1, IL-6, TNF-α |

Role of Corticosteroids on Symptoms

Dexamethasone is a synthetic glucocorticoid. It exhibits potent anti-inflammatory, immunosuppressant activity with minimal mineralocorticoid properties.
Preliminary Studies by our group and other investigators have found that Corticosteroids in cancer population can improve transiently pain, appetite, nausea, fatigue and overall quality of life. There are a number of different mechanisms have been proposed for these effects. These include reduction of the tumor mass [82-85]. Corticosteroids modulate

adrenergic activity in the dorsal horn [86]. Corticosteroid also can effect tumor function and decrease peritumoral edema (87].Corticosteroids also have analgesic properties [13-23], Central antiemetic and euphoric effects [(13,24-27]. Dexamethasone also suppresses abnormal discharges produced by injured somatic and autonomic nerves [88]. Dexamethasone decreases several inflammatory cytokines including IL-1, IL-6, IL-8 TNF-α, IFN, TGF-α. [28-33].

Fatigue

Fatigue is the most common symptom in patients with cancer or its treatment [89]. It is also a most undertreated symptom in patients with cancer [90]. Cancer-related fatigue results in substantial adverse physical, psychosocial, and economic consequences for both patients and caregivers [90]. This is a multidimensional syndrome resulting from a combination of factors including tumor by-products, host cytokines, cachexia, depression, anxiety, sleep disorders, and the effects of drugs or radiation therapy [91,92]. Corticosteroids decrease fatigue. The proposed mechanisms include (1) Decrease of the cytokines IL-1, IL-6, TNF-alpha and IFN- gamma that are involved in the causation of fatigue. [13-16,37,71,93-95], (2) Corticosteroids have an effect on on HPA axis function, as disturbances in HPA axis function have been observed in other chronic inflammatory and fatigue-related disorders [32,96].

Nausea and Anorexia:

Corticosteroids decrease nausea in advanced cancer patients [13]. The mechanisms by which steroids exert their antiemetic activity are not fully understood. When used in combination with other anti-emetics, they exert a booster effect in raising the emetic threshold. They decrease the peritumoral edema, thus the intracranial pressure, a known cause of vomiting. It is not evident that there is any difference between the different steroids, but dexamethasone appears to be the most intensively investigated. For prevention of acute emesis an 8 mg single dose of dexamethasone for moderately emetogenic chemotherapy and 20 mg for highly emetogenic chemotherapy should be the doses of choice. [24-27, 97-99].

Improvement in nausea, appetite and food intake potentially benefit in the management of cachexia. Several double –blind randomized controlled trials have demonstrated the symptomatic effect of different types and dosages of corticosteroids for cancer cachexia. [13,16-18,22, 100,101].

Pain

Corticosteroids such as Dexamethasone are beneficial in the management of many different types of pain in the palliative care settings. Based on extensive clinical experience, the accepted pain-related indications are refractory neuropathic pain, bone pain, pain associated with capsular expansion or duct obstruction, pain from bowel obstruction, pain caused by lymphedema, and headache due to increased intracranial pressure. Corticosteroids are also effective in managing pain and symptoms from metastatic spinal cord compression [Greenberg HS, et al, 1980; The analgesic effects of corticosteroids presumely result from a variety of mechanisms (1) Mass effect from expanding neoplasm could be lessened by the reduction of peritumoral edema (102), (2) antiinflammation. (13-23) and (3) immunosuppressant action. The effects of dexamethasone upon hyperalgesic activities of carrageenin, bradykinin, TNF-α. IL-1β, IL-6, IL-8, $PGE_2$, and dopamine were investigated in a model of mechanical hyperalgesia

in rats. The hyperalgesic responses to PI. injections of carrageenin, bradykinin, TNF-α, IL-β and IL-6, but not IL-8, $PGE_2$ and Dopamine were inhibited by pretreatment with dexamethasone (103).

Role of Corticosteroids on Cytokines

Patients with advanced cancer experience clusters of physical and psychosocial symptoms including pain, fatigue, nausea, anorexia/cachexia, depression, and sleep disorders. Cytokines and other pro-inflammatory mediators are elevated in patients with advanced cancer as a consequence of the presence of the tumor, the host response and co-morbidities such as infections or treatment interventions including drugs, radiation therapy and chemotherapy [6]. Several cytokines and pro-inflammatory mediators have been implicated in causing or amplifying some of these symptoms. Dexamethasone relieves symptoms associated with advanced cancer. These symptoms include pain, fatigue, anorexia/cachexia, and nausea. Dexamethasone decreases several cytokines including IL-1, IL-4, IL-6, IL-8 TNF-α, IFN, and TGF-α. [28,33,101,104,105]. The effects of dexamethasone upon hyperalgesic activities of carrageenin, bradykinin, TNF-α. IL-1β, IL-6, IL-8, $PGE_2$, and dopamine were investigated in a model of mechanical hyperalgesia in rats. The hyperalgesic responses to PI. injections of carrageenin, bradykinin, TNF-α, IL-β and IL-6, but not IL-8, $PGE_2$ and Dopamine were inhibited by pretreatment with dexamethasone (103).

| Author | Patients | Patient Treatment Duration (Study Design) | Daily Dosing scheme (equivalent study design) daily dose of Dexamethasone(DM) |
|---|---|---|---|
| Bruera et al 1995 | 40 | 14 days | MP* 32 mg (6mg) (Randomized double blind crossover) |
| Della Cuna 1989 | 40 | 8 weeks | MP* 125mg (23.44mg) (Randomized double blind placebo – controlled parallel) |
| Popiela et al | 173 | 8 weeks | MP* 125mg (23.44mg) (Randomized double blind placebo – controlled parallel) |
| Cassileth et al 1983 | 22 | 56 trials | 10mg (Randomized Controlled Trial Parallel) |
| Italian group for antiemetic research 2000 | 708 | 5 days | 8mg (Randomized double blind placebo – Controlled, parallel) |
| Akira Inoue 2003 | 68 | 6 days | 8mg (Randomized double blind placebo – Controlled, parallel) |

| | | | |
|---|---|---|---|
| Koo and Ang 1996 | 98 | | 8mg (Randomized double blind placebo – Controlled, parallel) |
| JR Hardy 2001 | 160 | 21.5 days | 12mg (survey) |
| Mercadante | 376 | 26 days | 4-16mg (survey) |
| Bruera 2004 | 51 | 7 days | 20mg (Randomized double blind placebo – Controlled, parallel) |
| Vecht 1994 | 96 | 28 days | 4-16mg (Randomized double blind placebo – controlled parallel) |

*MP= Methylprednisolone

**Significance:**

At present there are limited treatment options to treat these symptoms clusters. In clinical practice there is widespread acceptance of use of steroid therapy in treatment of advanced cancer patients with symptoms specifically pain, nausea, fatigue and anorexia. Preliminary research by our group and other investigators has found that Dexamethasone in cancer population can decrease transiently pain, appetite, nausea, fatigue and overall quality of life [Bruera and Roca et al 1985; Tannock I, etal 1996; Kim JH, Fainsinger et al., 1994; A.B. Ettinger et al 1988; T. Popiela, et al, 1989; Della Cuna, et al, 1989; Twycross, 1992; Mercadante, et al 2001; Vecht ChJ, et al 1989; Moertel C, et al., 1974; Stiefel FC, Breitbart WS, et al, 1989].

Despite it, the data is inadequate to draw definitive conclusions about the efficacy of the steroids in the management of pain and other symptoms in advanced cancer. The data collection and methodology was inadequate. Assessment tools were not validated, especially the term 'Activity' may not the accurate measure for fatigue. There was no attempt to understand the pathophysiology using laboratory correlates. The role steroids on cancer related fatigue, pain, appetite and nausea (which are the most common symptoms in advanced cancer), their effects on cytokines need to be defined through randomized controlled studies using updated and validated and laboratory correlates (which were lacking in the previous studies on corticosteroids for symptoms). Our findings will also allow investigators

- To effectively treat the symptoms clusters in advanced cancer patients and improve their quality of life.
- Establish cause and effect relationship between symptoms and cytokines.
- Development of cytokine specific suppressive therapies that could be used to prevent and treat Fatigue, nausea, anorexia and pain.

D. Preliminary studies

Studies on Symptom Management

Our group has conducted multiple studies on the treatment of difference symptoms in patients with advanced cancer. Specifically, we have conducted clinical trials of pain management using opioids [106], and adjuvant drugs [107]; fatigue using corticosteroid [13], methylphenidate [108], and donepezil [Bruer109]; cognitive failure using methylphenidate [108]; and anorexia/cachexia using megestrol acetate [110], fish oil [111], and thalidomide [112]. In the course of conducting these studies, we learned that patients presented with symptom clusters rather than using the main symptom target for our intervention.

**A. Experiences in the Assessment of Symptoms in Advanced Cancer Patients**

Our group has conducted multiple studies of symptom assessment in patients with advanced cancer. We developed the Edmonton Symptom Assessment System [113], a tool that has undergone independent validation [114] and is currently being widely used in acute care hospitals, hospices, and palliative care units. We have also developed the Edmonton Staging System for Cancer Pain [115], the Edmonton Functional Assessment Test [116].

Using these and other tools we conducted a number of studies on the frequency and severity of symptoms. In an outpatient setting, we evaluated 138 consecutive patients with advanced cancer referred to multidisciplinary palliative care clinic at M.D. Anderson Cancer Center, a cluster of symptoms was observed and the median symptoms intensity (0= no symptom, 10=worst symptom) was ranked as fatigue 7 (4.5-8), pain 6 (4-8), anorexia 6 (4-8), sleep problems 6 (4-8), drowsiness 5 (1.5-8) and anxiety 5(1-8)[117]. We retrospectively reviewed 320 patients referred to our palliative care inpatient unit, we observed that the main referral symptoms by the primary physicians were pain (44%), nausea (41%), fatigue (39%) and dyspnea (38%), the mean intensity ranked as fatigue 6.7 ± 2.7, pain 5.7 ± 3.5, anorexia 5.4 ± 3.4, sleep problems 5.0 ± 3.3[118]. In a tertiary acute care hospital, we retrospectively reviewed 100 consecutive cancer patients who had been referred to a palliative care consult team, we found that the most intense symptoms were fatigue, appetite and well-being [119]. We also found higher frequency and severity of symptoms in patients admitted to the community-based hospices [120].

Table IV summarizes the frequency of the main symptom clusters observed in different settings and also the frequency of patients who developed severe (≥ 3/10 intensity of these symptoms) [120].

Frequency of Severe Symptoms (ESAS ≥ 3/10) in the Different Settings

| Symptom | TPCU(%) | Acute Care (%) | Hospices (%) | p-value |
|---|---|---|---|---|
| Pain | 117/157 (75) | 295/642 (46) | 244/425 (57) | <0.0001 |
| Fatigue | 139/155 (90) | 559/625 (70) | 367/449 (82) | 0.0006 |
| Nausea | 56/153 (37) | 127/638 (20) | 92/382 (24) | 0.0001 |
| Depression | 88/149 (59) | 247/568 (43) | 183/408 (45) | 0.0026 |
| Anxiety | 103/153 (67) | 285/578 (49) | 213/420 (51) | 0.0003 |
| Drowsiness | 112/155 (72) | 397/623 (64) | 321/434 (74) | 0.0011 |
| Well-being | 119/148 (80) | 382/536 (71) | 274/422 (65) | 0.0013 |
| Appetite | 117/153 (76) | 503/617 (82) | 327/444 (74) | 0.0083 |
| Shortness of breath | 77/154 (50) | 203/633 (32) | 156/409 (38) | 0.0007 |
| Overall | 928/1377 (67) | 1998/5460 (55) | 2177/3793 (57) | <0.0001 |

*P* -values determined using chi-square test. Significance was accepted at the p<0.0055 level to take into account the Bonferroni correction for multiple comparisons.

Our findings show that symptom clusters as extremely frequent and that we have the methodology to appropriately determine the frequency, severity and relationship of those symptoms and the change over time and as a result of different treatment interventions.

By using the results of this study the Investigator would have a better understanding of the biological mechanisms of the symptom clusters. Hence treat the symptom clusters in

advanced cancer patients and thereby improve their quality of life. The understanding of the mechanisms would enable the Investigator in the future to develop cytokine specific suppressive therapies that could be used to prevent and treat these troubling symptoms.

Studies on cytokines

In our clinical studies with a number of cytokines in cancer patients, symptoms such as fatigue and constitutional symptoms such as pain, malaise, depression, and sleep disorders are commonly observed. Because many of the hematopoietic cytokines activate immune cells including monocytes, we examined the numbers and functions of monocytes and measurements of cytokines [121-124]. Our findings have shown that with cytokines that activate monocytes such as GM-CSF or PIXY-321 (fusion molecule of GM-CSF and IL-3), there is a significant increase in the levels of stimulated release of TNF-α and IL-1β, which can explain constitutional symptoms such as fever, myalgia, bone pain, and fatigue experienced by these patients [121,122]. Interestingly, in vivo administration of IL-1 which causes severe symptom distress including high fever, myalgia, pain, and cognitive impairment, results in induction of more cytokine in vivo as evidenced by an increase in the intra-cellular transcripts of IL-1 mRNA and an increase in the levels of cytokine in the supernatant of cells as measured by an ELISA assay (Fig 2a and b) [124].

Figure 2a

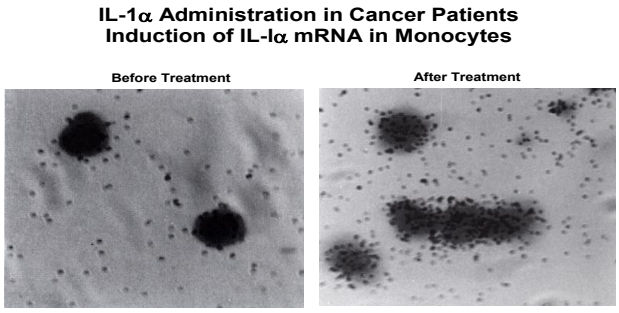
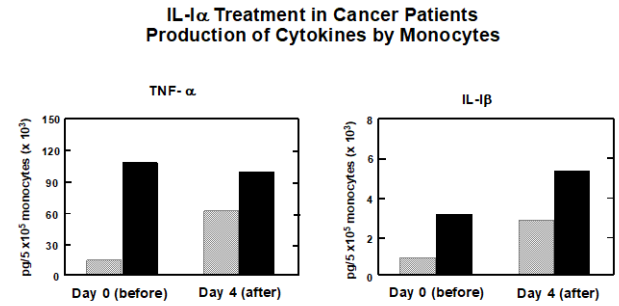



Figure 2b




Cytokine levels by Luminex method:

Recently, simultaneous measurement of multiple cytokines with a small sample size is made possible with the use of Luminex method. We have examined the levels of multiple cytokines in plasma of chemo-naïve patients with sarcoma. As shown figure 3 below, the preliminary results of these assays in a cohort of 8 patients showed that prior to treatment with chemotherapy, a number of endogenous cytokines are measurable in

the plasma of these cancer patients. After one cycle of chemotherapy, there is a marked decrease in the levels of Th-1 type of cytokines such as IL-2, IFN-gamma, and TNF-alpha. In contrast, the levels of IL-6, IL-8 and IL-10 were increased. We also examined the levels of IL-6 by ELISA to see if there was a correlation in the levels. As shown in the fig. 3 below, IL-6 levels were increased post treatment by both Luminex and ELISA methods. We plan to further examine the correlation between symptom distress experienced by these patients and the circulating levels of cytokines as patients undergo cytotoxic treatment. In the present proposal, we wish to examine the cytokine profile before the initiation of treatment with Dexamethasone and during treatment and at the end of the study with Dexamethasone vs. placebo, and sought correlation between the cytokine levels, symptom clusters, and response to Dexamethasone treatment.

E. Research design and Methods.

We will conduct a prospective, randomized, double blind, placebo controlled study comparing Dexamethasone 4mg orally two times per day for 14 days versus placebo. Eligible patients who agree to participate in the study and provide written informed consent will be randomized to either group A, in which patients will receive Dexamethasone orally, 4mg two times a day for 14 days; or group B, in which patients will receive placebo orally, two times a day for 14 days. On day 15, all patients will be receive 4mg of dexamethasone twice a day on a open label basis till Day 21,From Day 22 to Day28 the dose of dexamethasone is to be tapered to 2mg orally twice a day. Subsequently patients would be off study with dose tapered to the minimum tolerated dose.
The reason to have open label design after Day15 is to observe the descriptive trends.
Exam (including history including FACIT-F, FAACT, HADS, ESAS, BPI, GSE (on days 8, 22, and 29),physical exam and toxicity assessment will be done day 0(baseline), Day 8 [ ± 3 days], Day 15 [ ± 3 days], Day 22 [± 3 days] Day 29 [ ± 3 days]. ESAS and Toxicity will be done on day 4. A physician will do a physical exam on the patient on day 0, 15, and Day 29; and the nurse will do a nursing assessment on days 8, and day 22. 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, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels, C-reactive protein, complete blood counts, chemistry (electrolytes) within 7 days of baseline, Day 8 [ ± 3 days], Day 15 [ ± 3 days], Day 22 [ ± 3 days], and Day 29 [ ± 3 days]. If patients are unable to return to clinic on Day 8, 15, 22, or 29 the laboratory correlates will not be done. 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 $\pm$ 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.
The electrolytes measured will include chloride (Cl), carbon dioxide (CO2), Potassium (K) and Sodium (Na).

Treatment plan is illustrated in Figure 2.

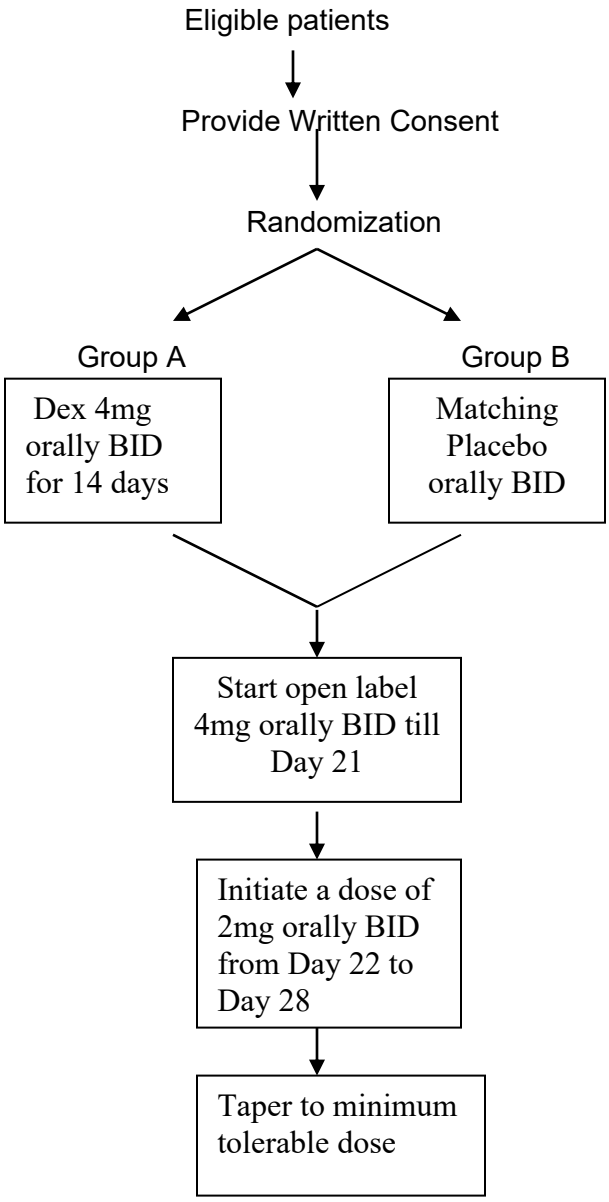



Figure 2.

| Assessments | Baseline | Day 4+ | Day 8 [± 3 days] | Day 15 [ ± 3 days] | Day 22 [ ± 3 days] | Day 29 [ ± 3 days] | Day 43 [± 3 days] |
|---|---|---|---|---|---|---|---|
| MDAS | X | | | | | | |
| | | | | | | | |
| BPI | X | | X | X | X | X | |
| FACIT-F | X | | X | X | X | X | |
| FAACT | X | | X | X | X | X | |
| HADS | X | | X | X | X | X | |
| r-ESAS | X | Y | X | X | X | X | PE or Y |
| GSE | | | X | | X | X | |
| Toxicity | X | Y | X | X | X | X | PE or Y |
| Demographics | X | | | | | | |
| Cytokine, Activated monocytes and corresponding receptor levels | Within 7 days | | X | X | X | X | |
| C-reactive protein | Within 7 days | | X | X | X | X | |
| Electrolytes (Cl, CO2, K, & Na), CBC | Within 7 days | | X | X | X | X | |
| MD physical exam | PE | | | PE | | PE | |
| RN assessment | | | A | | A | | |

X = assessment, Y=phone evaluation, PE= MD assessment, A= RN assessment

**Table. 1 Clinical and Laboratory Evaluation During Study**

Recruitment

H. Screening Measures

Symptom clusters and intensity: Patient must have 3 or more symptoms (fatigue, Pain, nausea, anorexia/cachexia, sleep problems, depression) based on Edmonton Symptom Assessment System, and the average intensity of each symptom during last 24 hours must be >/= 4 on a 0 to 10 scale (0 is no symptom, 10 is worst possible symptom). Target symptoms chosen for this study were based on previous research by our group and others, suggesting that Dexamethasone has potential effects on these symptoms. According to NCCN guideline, symptoms such as pain and fatigue are measured on a 0 to 10 numerical scale (0 is no symptom, 10 is worst symptom imaginable) can also be measured on categorical scale, none (0), Mild (1-3), Moderate (4-6) and Severe (7-10). We will include patients with symptom intensity >/= 4 (moderate or severe).

Clinical setting

Patients will be recruited from the Palliative Care and Rehabilitation Medicine, Pain center, and Thoracic center at M.D. Anderson Cancer Center. Patients will also be

recruited from LBJ hospital and at Four Seasons Hospice in Flat Rock, North Carolina. The physicians will identify potential eligible patients to participate in this study.

The Pain, and Symptom Care Palliative Care Clinics from which patients will be recruited at U.T. M.D. Anderson Cancer Center, operates out of the Pain and Palliative Care Center. There are 13 examination rooms staffed by 14 physicians and 5 clinical nurses, and 1 advanced practice nurse. Patients will be recruited from the Palliative Care Outpatient Clinic, which serves, on average, 227 patients a month, and the Pain Clinic, which serves about 464 patients a month. Patients will also be recruited from the Thoracic Clinic, which serves about a 1,000 patients a month. Services available through this clinic include thoracic and cardiovascular surgery, thoracic oncology, and radiation oncology. There are a total of 14 examination rooms staffed by 19 physicians and 11 clinical nurses, 7 advanced practice nurses.

Research staff
The research staff in the Department of Palliative Care and Rehabilitation Medicine at UT M.D. Anderson Cancer Center includes a research nurse manager, a biostatistician, two senior research nurses, one research nurse and one clinical data coordinator. Our group has conducted multiple clinical trials related to symptom management, quality of life and communications between patients and physicians.

***Eligibility Requirements***
Inclusion Criteria. Patients will be eligible to participate in this study if they meet the following criteria:

1. Present with 3 or more symptoms during the last 24 hours (pain, fatigue, chronic nausea and anorexia/cachexia, sleep problems, depression or poor appetite) with average intensity of >/= 4 on a 0 to 10 scale, in which 0=no symptom, and 10=worst possible symptom.
2. No clinical evidence of cognitive failure as evidenced by MDAS score of 13 or less at baseline.
3. Must be 18 years or older.
4. No longer a candidate for aggressive anticancer therapy such as receptor blockers (Iressa, etc.). Patients on oral or palliative chemotherapy are eligible for study if approved by primary oncologist prior to inclusion. Patients who are receiving IV chemotherapy are eligible for study if approved by primary oncologist and they have completed 1st cycle of chemotherapy and are deemed stable by primary oncologist. PI will obtain approval from patient's primary oncologist.
5. Life expectancy ≥ 30 days.
6. Must understand and sign written informed consent.
7. Patients on topical, or inhaled corticosteroids are eligible for study. If patients have been on oral corticosteroids for </= 7 days prior to inclusion of study they are eligible for study.
8. Patients currently taking Megestrol must be off drug for > 7 days prior to study inclusion

Exclusion Criteria.

1. Allergy to Dexamethasone,
2. Inability to complete the baseline assessment forms
3. Patients currently taking Megestrol, and not off drug for > 7 days

4. Anemia as defined as a hemoglobin of < 9
5. Known history of HIV
6. Neutropenia as defined by an absolute neutrophil count (ANC) of < 1500 cells/mm
7. Patients with a history of diabetes will be excluded.
8. All major surgeries such as thoracotomy etc., that requires wound healing within last 2 weeks.
9. Those who are currently receiving oral corticosteroid therapy or who have been on corticosteroid therapy >/= 8 days prior to study inclusion
10. Sepsis and/or acute, chronic, or ongoing infections

***Randomization***

Patients will be randomized to one of two treatment arms. One arm would have 50 eligible patients and would receive Dexamethasone and another would also have 50 eligible patients will receive matching placebo. The randomization schema will be based on parameters input into RANLST, a randomization program developed at MDACC and supported by an NCI grant. A randomization list containing order information for both arms will be made. Patient names in sequence will be recorded on each list as the patients are entered and both lists will match patient name and identification number. Only the primary statistician and Investigational Pharmacy will know the complete list of the order of randomization into the two arms until the end of the study. However, the code for an individual patient as to drug treatment group may be disclosed early and the patient removed from the study in the case of a request by the primary treating physician due to adverse events. Otherwise, no other persons will know about the assignment of patients to treatment arms until the end of the study.

**Outcome measures**

Specific aim #1: To determine the effect of Dexamethasone on the intensity of Fatigue
**We hypothesize that dexamethasone decreases the intensity of symptoms namely Fatigue, nausea, anorexia and pain that occur frequently in advanced cancer as compared with those receiving placebo**

1. **Measures of Fatigue**

The *patient* will rate symptom scores at baseline, day 8 [ ± 3 days], day 15 [ ± 3 days], day 22 [ ± 3 days], and day 29 [ ± 3 days], by using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (Appendix x): The FACIT-F fatigue subscale has been used primarily in cancer patients to measure fatigue. 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". 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) [125].

The *patient* will rate symptom scores at baseline, day 8 [ ± 3 days], day 15 [ ± 3 days], day 22 [ ± 3 days], and day 29 [ ± 3 days], by using the Edmonton Symptom Assessment System (ESAS) (Appendix x): This tool is designed by our group [Bruera et al., 1991] to assist in the assessment of nine symptoms common in cancer patients: pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, feelings of well-being and a line labeled "Other Problem". 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 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 [114]. The instrument is designed for both patient and caregiver (if the patient is cognitively impaired or for other reasons cannot independently do the ESAS) to complete [113].

**Specific aim #2:** To determine the effect of Dexamethasone on the intensity of Pain, anorexia and nausea

**Measures of pain : Brief Pain Inventory (BPI) Pain** severity and pain interference will measured with the BPI. The ***patient*** will rate symptom scores at baseline, day 8 [ ± 3 days], day 15 [ ± 3 days], day 22 [ ± 3 days], and day 29 [ ± 3 days]. The BPI asks patients to rate their pain for the last week on 0-10 scales at its "worst," "least," "average," and "now." The scales are presented in a 10 cm line, with each number equidistant from the next. Each scale is bounded by the words "no pain" at 0 end and "pain as bad as you can imagine" at the other. Using the same type of scales, patients are also asked to rate how their pain interferes with several quality of life domains including activity, walking, mood, sleep, work, and relations with others. These scales are bounded by "does not interfere" at the 0 end and "interferes completely" at the other. Patients are also asked to estimate the pain relief they are receiving from their pain treatment (in percent), to locate areas of pain on a human figure, and to estimate the cause of their pain (cancer disease, cancer treatment, or non-cancer). Issues of the validity and reliability of the BPI have been examined in detail [126,127].

**Measure of anorexia**: Symptom Measure (Cachexia/ Anorexia): Functional Assessment of Anorexia/Cachexia Therapy (FAACT). The ***patient*** will rate symptom scores at baseline, day 8 [ ± 3 days], day 15 [ ± 3 days], day 22 [ ± 3 days], and day 29 [ ± 3 days]. This 12 item Symptom-specific subscales in addition to FACIT-G is to measure patients additional concerns about their anorexia /cachexia. The FAACT has internal consistency and a reliability coefficient (Cronbach's alpha) of 0.88 for its 12 components [125]. Patients rate the intensity of anorexia/cachexia and its related symptoms on 0 to 4 numerical scales from 0 "not at all" to 4 "very much".

**Measure of anorexia:** the ESAS tool that was used for the measurement of fatigue also measures nausea.

**Specific aim # 3:** To determine the changes in cytokines (IL-1, IL-6, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels) and C-reactive protein before and after treatment with dexamethasone.
We **hypothesize** that dexamethasone decreases the intensity of symptoms namely Fatigue, nausea, anorexia and pain that occur frequently in advanced cancer and one of the mechanisms it exerts such effects by decreasing a cytokines levels (namely IL-1, IL-6, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels) and C-reactive protein that mediate these symptoms.

**Specific aim #4:** To collect pilot data on the quality of sleep and cortisol levels in ten subjects.

Measure of sleep quality: The Pittsburg Sleep Quality Index (PSQI) will be used to measure subjects' sleep quality. The PSQI (Appendix N) is a 9-question, 19 item self-report instrument designed to measure sleep quality. PSQI questions 1-4 request specific respondent information that is filled in by hand, such as customary bed time and length of time to fall asleep. PSQI questions 5-8 are answered on a 0-3 scale with 0

indicating no symptom presence and 3 representing symptom presence 3 or more times the past week. Question 9 is answered on a 0-3 scale with 0 meaning “very good” and 3 representing “very bad.” All scores are combined according to the scoring criteria included with the form to produce a Global PSQI Score. Scores above 5 indicate clinically meaningfully disturbed or poor sleep.

Cronbach’s alpha coefficient produced an average internal consistency reliability estimate of .80 for the Global PSQI Score across numerous patient populations with a variety of different physical ailments. Additionally, the PSQI is more highly correlated with sleep problems (r =.69-.77) than with unrelated constructs, such as mood symptoms and depression (r =.22-.65). Additionally, Global PSQI Scores above 5 resulted in a sensitivity of 98.7 and specificity of 84.4 to persons with sleep disturbances versus controls. (http://www.bmedreport.com/archives/6559)

Salivary cortisol levels were assessed by enzyme immunoassay (Salimetrics, State College, PA http://www.salimetrics.com/products and_services/salivary_assays/specifications/cortisol.php ). This assay has a lower detection limit of less than 0.003/dL. The mean intraassay coefficient was 5.5 (range, 4–6%) and the mean interassay coefficient was 8.2 (range, 7–11%). All samples from a participant were analyzed in duplicate in the same assay to minimize variability. Appendix O explains the testing protocol.

**Cytokine Measures**

Cytokine-antagonists that inactivate pro-inflammatory cytokines such as TNF (e.g. Ethanercept), IL-1 (e.g.IL-1ra), and IL-6 (anti-IL-6 antibody) have been investigated in trials in which an aberrancy in cytokines has been found [121]. Cytokines such as IL-1, IL-6, TNF-α, and IFN-α have been reported to be correlated with other symptoms such as pain, anorexia/cachexia, depression, cognitive impairment and sleep disorders in cancer patients. Thus, measuring levels of cytokines and examining them for a possible correlation with symptom clusters, and the response to Dexamethasone may provide insight into the pathophysiology of symptom clusters experienced by patients with cancer and may reveal novel strategies to overcome these distressing symptoms.

In this study, we will measure the levels of IL-1β, IL-6, TNF-α, IL-10, IL-8, activated monocytes and corresponding receptor levels) and C-reactive protein at baseline, 8 [ ± 3 days], 15 [ ± 3 days], 22 [ ± 3 days], day 29 [±3 days]. The serum samples will be stored frozen for subsequent cytokine profile. Serum samples will be assayed. The cytokine profile will be correlated with the degree of symptoms and for the responsiveness or failure to respond to Dexamethasone. As high levels of plasma IL-1 β, TNF-α, IFN-γ and IL-6 are associated with sleep disturbance, nausea, and weight loss, any significant reduction in these cytokines will result in appreciable reduction in these symptoms.

Pro-inflammatory cytokines (IL-1, IL-6, TNF-α) will be measured in the serum of patients using commercially available Luminex kit (Biosource Inc.). The Multiplex Bead Immunoassay will be used to measure serum/plasma levels of IL-1, IL-6, IL-10, IL-8, activated monocytes and corresponding receptor levels, and TNF-alpha. This assay sensitivity for the cytokines is 3-6 pg/mL. The Multiplex Bead immunoassay represents the development of a Multiplex Assay designed to work in conjunction with the Luminex 100 analyzer (Luminex Corp., Austin, TX), associated software and fluorescently encoded microspheres. In this assay, each microsphere is labeled with a distinguishable fluorophore that allows it to be assigned or gated to a particular region by

the scanner. Antibodies, specific for the cytokine or protein of interest (purchased from Biosource International, Camarillo, CA) are covalently linked to individually beads of a different fluorescent marker. When the beads are reacted with sera or plasma containing cytokines, the cytokines bind to the bead coated with the complementary antibody, and its unique fluorescent signature can detect cytokine-bead complex by the Luminex 100 analyzer. These assays have been performed in our laboratory in support of our ongoing trials.

If the levels of any or all of the inflammatory cytokines are found to be elevated and significantly correlated with the degree of symptoms and correlation with the response or failure to respond to dexamethasone treatment, it may provide directions for future strategies to be explored such as cytokine blockers or antagonists in combination with dexamethasone or other novel agents. We would be interested in designing such study based on the rationale from laboratory investigations

The absence of elevated levels of cytokines in circulation may not rule out their possible role in the cytokines in pathophysiology of symptom clusters. It is possible that local cellular production of cytokines may be responsible for symptoms. In the absence of a conclusive correlation between plasma cytokines, magnitude of symptoms, and response to Dexamethasone, we will separate the mononuclear cells and freeze cell lysate for future analysis of intra-cellular measurements of cytokines.

**Specific aim #4**: To determine association of cytokines (IL-1, IL-6, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels)) and C-reactive protein and Fatigue, Pain, Anorexia and nausea.

**We will also investigate how cytokines and C-reactive protein are related in combination to the symptoms of fatigue, pain, anorexia, and nausea. These analyses will be made separately for each symptom. We will use a repeated measures analysis with the change in symptom score between baseline and two weeks as the dependent variable, with the cytokines (IL1, IL6, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels) and C-reactive protein as independent variables, over three time points. Differences overall between groups will also be tested by this model, in addition to a test of a time effect and a group by time interaction effect.**

**Other Assessments**

- **Symptom Measure (Depression): Hospital Anxiety and Depression Scale (HADS):** This 14 item questionnaire has been validated in a number of clinical situations and has been widely used in medically ill patients [129], Although its use in cancer patients has been somewhat limited, we believe its proven validity in the clinical setting makes it well-suited for our study.
- **Global Symptom Evaluation.** This instrument is to estimate the minimal important difference in symptoms before treatment and after treatment. Patients will be asked about their symptoms (worse, about the same, or better) after starting new medication. If their answer is better, patients will be asked to rate how much better their symptoms are (almost the same, hardly any better at all, a little better, somewhat better, moderately better, a good deal better, a great deal better, a very great deal better). If their answer is worse, patients will be asked to rate how much worse their symptoms are (almost the same, hardly worse at all, a

little worse, somewhat worse, moderately worse, a good deal worse, a great deal worse, a very great deal worse) [130,131].

- **Toxicity Assessment**: The potential side effects of Dexamethasone will be assessed using the side effects recording sheet based on NCI common toxicity criteria.

- **Demographic variables.** The variables of age, gender, education, race, and ethnicity, cancer diagnosis will be assessed at baseline.

**STATISTICAL CONSIDERATIONS**

Prior to inferential procedures, extensive descriptive statistical analyses of the outcome and predictor variables will be conducted. Standard descriptive statistics including means, standard deviations, ranges, and frequencies, together with 95% confidence intervals, will be computed where appropriate. Distributional characteristics of relevant variables will also be more closely examined using boxplots and histograms. If the data do not appear to be approximately normally distributed, transformations will be made to the data. Bivariate associations will be explored using Pearson's Product Moment correlation coefficients, scatterplots, and contingency tables.

The primary objective of this study is to determine the effectiveness of dexamethasone as compared to placebo after two weeks for the management of cancer-related fatigue. Fatigue will be measured using the Functional Assessment for Chronic Illness Therapy-Fatigue (FACIT-F), previously described. The FACIT-F has been validated in the assessment of fatigue in cancer patients. The current study will determine if the average decrease in fatigue from baseline to day 15 in patients who receive dexamethasone is greater than for patients who receive placebo.

In a pilot study testing the effectiveness of methylphenidate for the management of cancer-related fatigue in 30 patients, the variable fatigue was also measured at baseline and one week using the FACIT-F. The study showed that the baseline average of fatigue for 30 patients using the FACIT-F was 17.5 (11.3 standard deviation), and this average improved to 34.7 (10.0 SD) at day 7. This is an improvement of more than 1.5 standard deviations. The average difference score (matched by patient) was 17.1 with a standard deviation of 13.95. Therefore the change, by patient, between baseline and 7 days was about 1.2 standard deviations.

However, we are investigating a different drug in this study, and we also assume that there may be a placebo effect. Patients who receive placebo may improve in their fatigue scores. We propose to detect a decrease in fatigue in the dexamethasone group over and above that in the placebo group of ½ standard deviations, or approximately 7 on the FACIT-F scale. In order to declare this difference to be statistically significant, assuming a one-sided significance level of 0.05 and 80% power, we will need to enter 50 evaluable patients per group into this study. Twenty patients will be recruited at Four Seasons Hospice. We will enter a total of up to 160 patients to allow for a possible 37% dropout rate. A t test will be used to evaluate the difference between groups unless the data appear to be non-normally distributed, in which case a Wilcoxon rank-sum test will be used to evaluate the difference between groups. We will add performance status as a covariate in analysis if there are differences between the two groups.

Fifty evaluable patients per group will also allow us to detect a difference between groups for other symptom variables (of pain, anorexia and nausea) of approximately one-half a standard deviation (assuming a one-sided significance level of 0.05 and 80% power), or approximately 0.57 standard deviations for two-sided tests. Analyses will be made as above for fatigue. The variable pain will be assessed using the BPI, anorexia will be assessed using the FAACT, and nausea will be assessed using the ESAS.

Given that we will also have measurements available at 8 days (in addition to baseline and two weeks later), we will also conduct a repeated measures analysis of variance on each of the symptom variables. These analyses will include main effects of group and time (with three time points) and an interaction term of group by time. In addition, information will be graphically summarized by group for all days, including days 22 and 29, when dexamethasone will be provided open label.

The third objective will determine if there is more of a change over time in cytokines for the group that receives dexamethasone as compared to the placebo group. Analyses will be similar to those made for the symptom variables. We will initially analyze difference scores between baseline and two weeks later by use of a t test if the data are approximately normally distributed and by a Wilcoxon test if not. We will also conduct analyses using a repeated measures analysis of variance with time points of baseline, 8 days and two weeks later. As above these analysis will include main effects of group, time, and a group by time interaction.

The associations between symptom and cytokine change scores at two weeks from baseline will also be explored. We will determine the correlations between all combinations of the symptoms of fatigue, pain, anorexia and nausea, the cytokines IL1, IL6, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels, and C-reactive protein. If the data are approximately normally distributed we will use a Pearson's correlation coefficient to measure these associations, and otherwise will use a Spearman's correlation coefficient. If necessary, we will transform the data to achieve approximately normal distributions. Our initial hypothesis is that when symptoms increase in severity, cytokine levels also increase. We will be able to declare correlation coefficients greater than 0.39 as statistically significant with a two-sided significance level of 0.05 and 80% power.

We will also investigate how cytokines and C-reactive protein are related in combination to the symptoms of fatigue, pain, anorexia, and nausea. These analyses will be made separately for each symptom. We will use a repeated measures analysis with the change in symptom score between baseline and two weeks as the dependent variable, with the cytokines (IL1, IL6, TNF-$\alpha$, IL-10, IL-8, activated monocytes and corresponding receptor levels) and C-reactive protein as independent variables, over three time points. Differences overall between groups will also be tested by this model, in addition to a test of a time effect and a group by time interaction effect.

Summary information on the global symptom evaluation by group will also be provided at each of the assessed time points. Differences in distributions between groups will be analyzed using a chi-square analysis.

When a total of 50 patients (one-half of total number of evaluable patients) have been entered and evaluated, the statistical collaborator will conduct an interim monitoring of efficacy and toxicity. Results will be presented overall and by arm retaining the blinding as to arm assignment. The PI and other collaborators (other than the statistical collaborator) will remain blinded as to the arm assignments of patients. We plan to stop

the trial at the time of interim analysis if the two groups differ in their reduction in fatigue from baseline to day 15 with a significance level less than 0.001. This would occur if differences in the reduction in fatigue were greater than twice the standard deviations of the groups, with 80% power. Toxicity is not expected in either group, but will also be summarized and monitored**.**

We will also determine on an exploratory basis whether patients increase or decrease their symptom levels from the end of the second week to the end of the third and fourth week. After week two patients will be aware that they are receiving the drug and not possibly a placebo. These analyses will be made separately by treatment group and summarized graphically. We will also conduct analyses at 3 and 4 weeks using the patient's 2-week score as a baseline. These analyses will consist of a t test or a Wilcoxon test as appropriate. If there is no carry-over effect, there should be no difference between the two groups in these analyses.

As a preliminary analysis repeated-measures analysis of variance will be used to examine correlation between salivary cortisol, cancer related fatigue (FACIT-F), sleep quality (PSQI) and cytokines (IL-1B, IL-6, TNF-A, IL-8, IL-10 and their receptors.

Missing Data

In order to allow for up to 37% of the patients to potentially drop out before completing the study for 15 days, we will recruit a total of approximately 80 patients per arm, or a total of up to 160 patients. After 7 days of our open pilot study of methylphenidate [37] we found that 30 out of 31 eligible patients were evaluable (97%). By day 28, only 21-30 patients remained evaluable (70%). Therefore, we estimate that the drop out rate could increase from 3% by day 7 to 30% by day 28. Since the duration of this study is of 15 days, we conservatively estimate that the dropout rate will be approximately 15% upon completion of the double-blind phase. However, as the study progresses, we are finding an actual dropout rate of 37% (43 out of 115).

Information from the intervention phase (days 15-29), where all willing patients will receive study drug, will be summarized and exploratory analyses conducted to determine if patients in the treatment group continue to experience reduced fatigue and if patients previously assigned placebo improve. However, the dropout rate after 15 days could be greater than 30% and sicker patients may be more likely to drop out early. Therefore the conclusions from these analyses may be preliminary only. However, this data set will also be used to determine the impact of different methods of taking into account data that may not be missing at random.

As an alternative analysis, subjects who drop out during the study will have their last available scores from the outcomes measures carried forward. This procedure will be used because subjects may in some cases drop out because of worsening disease, which may be reflected in their fatigue measures. Failure to account for this might otherwise bias the treatment effect estimate.

We will initially assume that missing data will give unbiased estimates of the intervention effects provided that the probability of having missing data depends only on the covariates in the model. We will check this assumption by looking at predictors of missing data. If the assumption is violated we will perform sensitivity analyses to determine the effect of varying the assumptions about the mechanisms for missing data. Other methods of accounting for missing variables will also be employed in sensitivity

analyses (132).

*a.* **Human Subjects**

This application is to obtain support for a clinical trial that will determine whether Dexamethasone at low doses can improve symptom clusters in patients with advanced cancer as compared to placebo; to determine whether the levels in serum of cytokines (IL-1, IL-6, TNF-α, IL-10, IL-8, activated monocytes and corresponding receptor levels) and pro-inflammatory marker CRP are associated with the symptom cluster score, before and after treatment with Dexamethasone.

Protection of Human Subjects

1. Permission to conduct the study under this grant will be obtained from the Institutional Review Board of M.D. Anderson Cancer Center. The Protection of Human Rights Guidelines will be followed during all study-related activities.
2. The proposed clinical trial will enroll patients. The inclusion criteria include the following: patients present with 3 or more symptoms (pain, fatigue, appetite (anorexia/cachexia), and nausea) during the preceding 24 hours, have an average intensity ≥4 on a 0 to 10 scale, in which 0=no symptom, and 10=the worst possible symptom;; have no clinical evidence of cognitive failure, have normal Memorial Delirium Assessment Scale [MDAS] 13 or > is considered as normal); must be 18 years or older; have life expectancy ≥ 6 weeks; have a negative pregnancy test if women with childbearing potential; must understand and sign written informed consent; have no concurrent steroids or be off steroids for at least 7 days prior to inclusion into study; Exclusion criteria include patients have major contraindication to Dexamethasone, i.e. allergic reaction; are not able to complete the baseline assessment forms and are pregnant or lactating.
3. Data collected for the clinical trial will be from patient medical charts, assessment tools and laboratory results. Data will be collected specifically for this research purposes, and existing data from medical charts will be incorporated (i.e., demographic data).
4. Patients will be informed that refusing to participate in the study or deciding to terminate their participation will not affect their current treatment plan. The patients will be given a written and verbal description of the study during the informed consent teaching interview. Guidelines regarding Institutional Review Board, Human Rights Protection will be strictly followed.

5. Study subjects will sign an IRB-approved written informed consent form after having the study explained to them in person by the physician. Included in this explanation will be a reassurance that lack of participation in the study will not bear a relationship to their care for cancer or its symptoms. Circumstances of obtaining informed consent will be documented in patient medical records. Informed consent will be obtained in the language preference of the potential subject. When necessary, professional translators, and not family members, will obtain written informed consent.

6. The most serious side effects known with dexamethasone is Cardiovascular: Edema, hypertension, arrhythmias, cardiomyopathy, myocardial rupture (post-MI), syncope, thromboembolism, thrombophlebitis, vasculitis. Central nervous system: Insomnia, nervousness, vertigo, seizures, psychosis, pseudotumor cerebri (usually following discontinuation), headache, mood swings, delirium, hallucinations, euphoria. Dermatologic: Hirsutism, acne, skin atrophy, bruising, hyperpigmentation, pruritus (generalized), perianal pruritus (following I.V. injection), urticaria.Endocrine &

metabolic: Diabetes mellitus, adrenal suppression, hyperlipidemia, Cushing's syndrome, pituitary-adrenal axis suppression, growth suppression, glucose intolerance, gynecomastia, hypokalemia, alkalosis, amenorrhea, sodium and water retention, hyperglycemia, hypercalciuria, weight gain. Gastrointestinal: Appetite increased, indigestion, peptic ulcer, nausea, vomiting, abdominal distention, ulcerative esophagitis, pancreatitis, intestinal perforation. Genitourinary: Altered (increased or decreased) spermatogenesis. Hematologic: Transient leukocytosis. Hepatic: Transaminases increased, hepatomegaly. Neuromuscular & skeletal: Arthralgia, muscle weakness, osteoporosis, fractures, myopathy (particularly in conjunction with neuromuscular disease or neuromuscular blocking agents), tendon rupture, vertebral compression fractures, neuropathy, neuritis, parasthesia. Ocular: Cataracts, glaucoma, exophthalmos, intraocular pressure increased. Miscellaneous: Infections, anaphylactoid reaction, anaphylaxis, angioedema, avascular necrosis, secondary malignancy, Kaposi's sarcoma, intractable hiccups, impaired wound healing, abnormal fat deposition, moon face. Topical:<1%: Itching, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, skin maceration, skin atrophy, striae, miliaria, local burning, irritation. secondary infection

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

Benefits: Several potential benefits may result. The study may provide data that will help us further understanding of symptom clusters, pro inflammatory mediators and symptom management.

Inclusion of women and minority

The subject selection procedure provides equal access to both genders. M.D. Anderson Cancer Center data suggest approximately equal gender distribution for the Pain clinic, Palliative Care & Rehabilitation Medicine clinic and thoracic clinic**.** Eligibility criteria do not exclude by race or ethnicity. We will collect detailed information on race and ethnicity by asking the subjects to self-identify or self-report ethnicity. Subjects will be ethnically diverse. All of the patients will be recruited at The University of Texas M. D. Anderson Cancer Center or Lyndon Baines Johnson Hospital in the breast surgical oncology clinic. During 2004, the population was approximately 71% Anglo-American, 11% African-American, 11% Hispanic, and 7% Asian/other. We believe that our sample will reflect the ethnic and racial, and gender demographics of the patients seen at MD Anderson and LBJ Hospital.

Target/Planned Enrollment Table: Total of 100 patients will be enrolled.

| Ethnic Category | Females | Males | Total |
|---|---|---|---|
| Hispanic or Latino | 5 | 6 | 11 |
| Not Hispanic or Latino | 43 | 46 | 89 |
| Ethnic Category: Total of All Subjects | 48 | 52 | 100 |
| **Racial Categories** | | | |
| Asian and other | 4 | 3 | 7 |
| Black or African American | 5 | 6 | 11 |
| Caucasian | 40 | 42 | 82 |

| | | | |
|---|---|---|---|
| Racial Categories: Total of All Subjects | 49 | 51 | 100 |

**Data and Safety monitoring**
The Institutional Review Board (IRB) of the University of Texas M. D. Anderson Cancer Center (MDACC) reviews and approves the Data and Safety Monitoring Plan for all clinical trials. In addition to ongoing monitoring by the PI and research staff, data and safety monitoring for this project will be conducted by two independent MDACC entities set up specifically to address these issues, the IRB and the Data Monitoring Committee (DMC). Plans and procedures for maintaining data integrity, defining and reporting adverse events/experiences, and IRB and DMC oversight and monitoring of this project are described below. These procedures include monitoring of participant eligibility and accrual, adverse events, interim data analyses, etc. The procedures for monitoring by the IRB and DMC are described in separate sections below, followed by a section defining and further describing procedures for reporting adverse experiences, for assuring that any action resulting in a temporary or permanent suspension of the trial is reported to the grant program director, as well as procedures for ensuring data quality and integrity.

***Monitoring the Progress of Trials and the Safety of Participants***
**Monitoring by IRB** During the protocol review and approval process, the IRB determines the level of safety monitoring required for each protocol. The minimum monitoring requirements include investigator monitoring of participant safety, adverse event (AE) reporting in compliance with IRB, NIH, and FDA guidelines, and participation in the Continuing Review process with the IRB. The Data Monitoring Committee (DMC) also monitors clinical trials. The outcomes of IRB and DMC reviews are conveyed to the PI via the administrative support staff in the Office of Protocol Research (OPR).

For all protocols conducted at the MDACC, the PI is responsible for submitting AEs to the IRB. The MDACC's policy for AE submission has been defined and approved by the IRB and must be included as an appendix to all protocols. AEs are submitted to OPR, entered into the Protocol Data Management System (PDMS) and forwarded to the designated IRB vice chairperson for review. Attached to each AE, is a listing of all prior AEs submitted for that protocol. Any comments, questions or changes the IRB requests to the protocol as a result of this review are conveyed to the PI. The PI response and protocol modification process is monitored by the IRB vice chairperson and OPR support staff. The vice chairperson presents the report on AE review to the full committee at the next IRB meeting.

All protocol participants must be registered in the Protocol Data Management System (PDMS). PDMS is a clinical trials database designed to meet the regulatory needs of the MDACC clinical research enterprise, allow PIs to collect their protocol data electronically, and allow electronic data transfer to NIH and industry sponsors. The Office of Protocol Research (OPR) creates a file in PDMS of each human subjects protocol submitted for review and approval. After the title, PI, collaborators and other protocol specific information is entered, the system assigns the protocol a unique number that will be used to track the protocol through review and approval, participant registration, adverse event collection, continuing review and participant data collection processes.

The system tracks the reviewers and the committee dates and outcomes of each protocol through the scientific review and IRB review processes. Once the protocol has IRB approval and all other issues are satisfied, the protocol may be “activated”. The Activation Process involves entering into PDMS the eligibility criteria, any dose information, and the date of the most current IRB approved informed consent document. Once activated, participants may be registered in the database. Activation is an independent step in the review and approval process and must be specifically requested by the PI.

It is the MDACC policy that all participants in a clinical trial must be registered in PDMS. To register a participant, the PI or research coordinator must enter some demographic data and then answer all the eligibility criteria that are specific for that protocol. The system is programmed with the logic to determine which eligibility criteria are not met based on the Yes/No response of the person registering the participant. For protocols sponsored by NIH, no participant may be registered unless they completely meet all eligibility criteria. This real time, continuous monitoring of participant eligibility increases participant safety by ensuring that only individuals that meet the criteria are enrolled.

PDMS also contains a field that is visible during the participant registration process that indicates the date of the current IRB approved informed consent document. The OPR staff updates this field each time the IRB approves a modification to an informed consent document. The IRB approved informed consent document is stamped dated and signed only when a protocol is activated. No document without the stamp can be used. Stamping, signing and dating the document are the final step in the activation process. Comparing the date on the informed consent document with the date in PDMS enables the registering individual to make sure the correct informed consent document was used.

OPR also uses PDMS as a tool for monitoring participant safety using menus designed for reporting, tracking and reviewing adverse events. All adverse events (AEs) submitted to the IRB are submitted to OPR, which provides the administrative support to the committee. Each AE for a participant treated at MDACC is entered into PDMS in the electronic file for the protocol upon which the participant was enrolled. The AE form and any additional information supplied to OPR are forwarded to an IRB Vice Chair who is responsible for reviewing AEs. In addition to the submitted information, a report is generated from PDMS summarizing all previous AEs submitted for that protocol and supplied to the IRB Vice Chair. This allows the reviewer to see the entire safety history of the protocol and identify trends much sooner than in situations where the safety information is reviewed together only once a year during an IRB review.

It is during this continuous AE review that the IRB requests PIs to make modifications to informed consent documents if new safety issues arise, or to request dose modification to reduce potential toxicity to the participant or any other protocol modification to enhance participant safety. This real time, continuous AE review and protocol/informed consent modification process is an important component of the MDACC continuous monitoring of participant safety.

Part of the information in the database for each protocol is the maximum accrual approved by the IRB. Since each participant is registered on the protocol in the database, monitoring the progress of the research by examining protocol accrual is a simple and routine process carried out by OPR. Every six months reports are generated for categories of Low, Slow, No Accrual and Approved but not yet activated. The PI of any protocol that falls in one of these categories is sent a memo requesting input on why the protocol is not accruing at the expected rate. Depending on the response, the

outcome is either closure of the protocol, or the protocol may continue for six months and be re-reviewed at that time.

In addition, PDMS sends an automatic email message to OPR who in turn notifies the PI when a protocol is within 5 participants of reaching maximum accrual. The system sends another email message when accrual is reached and OPR then closes the protocol to new participant entry. With this system, protocols cannot accrue participants in excess of the numbers approved by the IRB.

PDMS is also used in other ways as an audit tool by OPR. In addition to auditing eligibility, the evaluability, on-study dates, and off-study dates are all required entry fields and can be tracked on all research subjects through this computer system.

OPR performs audits on both a random and for-cause basis although its major focus is the operation of an elaborate and intense training program for research coordinators. It is the belief of the Office of Research Administration that while auditing can identify problems, education can prevent them. That is why that office has used OPR to stress an educational, proactive approach to research quality.

In addition, OPR contains an ombudsman function that confidentially assists research personnel who believe that a study may not be operating in a manner consistent with Good Clinical Practice. A report to this function may trigger an audit or some other type of investigation. Every report is investigated fully and confidentially to assure no repercussions to the reporter or to the research team performing the research in question unless a true violation is identified.

Most Phase 1 and 2 trials at M.D. Anderson are monitored on a day-to-day basis by the research teams performing the research. In addition the IRB may require frequent reporting on toxicity of any trial the IRB identifies as having risks warranting an increased monitoring frequency.

The requirements for AE reporting are extensively reviewed with all key personnel on grant applications during the mandatory IRB-sponsored training. In addition, every protocol must have the AE reporting requirements attached to it prior to IRB approval.

Every AE report is reviewed by a Vice Chairperson of the IRB and duly reported to the entire IRB at the next meeting. IRB meetings occur every two weeks. If immediate action is required (protocol closure, information dissemination to other PI's doing studies with similar agents) that is done by the IRB Vice Chair via the Office of Protocol Research. All of these actions are coordinated through the PDMS computer system.

Plans for assuring that that any action resulting in a temporary or permanent suspension of an NIH-funded clinical trial is reported to the NIH grant program director responsible for the grant.

For the most part, the closure of the trial will occur due to actions coordinated within the OPR, whether this is due to a poor audit, an IRB action, or unexpected AEs. OPR will work with the IRB to notify all parties requiring such notification (e.g., NIH, FDA, sponsor).

Audits are performed by the OPR on individual trials and accrual is monitored every six months on all trials.

**Monitoring of data at additional sites**

Since neither the UTMDACC IRB nor the OPRQA monitoring teams provide oversight or monitoring for the conduct of clinical trials conducted outside of UTMDACC, we will monitor the conduct of this trial at Four Seasons Hospice. The Four Seasons Hospice has submitted the protocol, and their IRB has already reviewed and approved the protocol. Data and safety monitoring at Four Seasons Hospice is consistent with the approved Data and Safety Monitoring Plan outlined in the protocol. The UTMDACC DMC will be used, and all data will be submitted to UTMDACC.

In order to uphold good quality research and monitor safety and quality data from outside institutions, we have established departmental procedures that will be implemented in these collaborations. With study activation, we plan to have orientation via teleconference, with involvement of the P.I., research data coordinator, research nurse and data manager, and plan for a future site visit by a member of the research team in order to provide for sufficient review of the protocol. CRF's will be submitted to UTMDACC in a timely fashion. With close monitoring of adverse event reporting, we would be able to maintain safe and quality study conduction with additional sites.

**MONITORING BY THE DATA AND SAFETY MONITORING BOARD:**

The Data Monitoring Committee(DMC) is an officially constitueted committee of MDACC designed to oversee the data and safety monitoring of clinical trials. The primary objectives of DMC are to:

- Ensure that participants in a trial are protected;
- Ensure that participants' interests are not made secondary to the interests of the scientific investigation; and
- Monitor all clinical trials that originate at MDACC or that are coordinated or analyzed by the MDACC.

  The DMC has the following responsibilities to accomplish the above objectives:
- To review interim analyses of outcome data (prepared by the study Statistician or other responsible person at the time points defined in the protocols approved by the IRB), and to recommend, if necessary, whether the study needs to be changed or terminated based on these analyses;
- To determine whether and to whom outcome results should be released prior to the reporting of study results from this trial at the time specified in the protocol;
- To review interim toxicity data and efficacy of treatment;
- To review major modifications to the study proposed by the PI prior to implementation (e.g., termination, dropping an arm based on toxicity results from this trial or results of other trials, increasing target sample size);
- To communicate information and recommendations to appropriate persons at MDACC regarding the assessment of issues or problems and effective resolutions for educational purposes and improved participant care and risk prevention.

The Committee consists of not more than 15 members (including the Chairman). A majority of members attending meetings of the DMC constitute a quorum. Appointments are made based on the breadth of backgrounds and experience. The committee includes scientists and statisticians from within and outside the institution selected based on their experience, reputation for objectivity, absence of conflicts of interest, and knowledge of good clinical trial methodology. At least fifty one percent of the voting members are not affiliated with MDACC. DMC members represent participant interests, and not that of the institution.

The DMC meets at least once a year, and more often if necessary. Each randomized clinical trial protocol has specified interim analyses times. Information provided to the DMC include: title of study, PI, date start of study, expected termination date, expected total number of participants, number of participants entered currently, data from interim analyses, date of interim analyses, toxicity concerns, and the next formal monitoring date as specified in the protocol. The PI may prepare a report addressing specific toxicity concerns or other concerns about the conduct of the study during the open session. A copy of the statistician's report may be sent to the DMC Chair for presentation during the closed portion, but not to any other individuals not on the DMC. The report may contain recommendations on whether to close the study, whether to report the results, whether to continue accrual or follow-up and whether DMC discussion is needed.

The review of each trial may include two parts. The first part will be an open session in which members of the study team may be present at the request of the DMC to answer questions. In this part, the focus is on accrual, compliance and toxicity issues. Following this open session, there will be a closed, executive session in which the DMC discusses interim outcome results by treatment arm, what action needs to be taken, and then votes. At the executive session, those present are limited, to DMC members, alternates, and ex officio members. If a decision is made by the DMC to modify or discontinue a trial - recommendations will be made as to whether and how participants are to be informed and by whom and communicated to the PI in writing. Copies of such communication will be preserved in the official Committee Minutes.

DMC recommendations are based upon results for the current study being monitored as well as upon data available to the DMC from other related studies. The PI will assure that the DMC is advised about relevant non-confidential results from other related studies that become available. It will be the responsibility of the DMC to determine the extent to which this information is relevant to decisions to continue or modify the current study. The DMC will provide recommendations in writing to the PI to change or stop a study, or part thereof (e.g., one arm), or to continue a study unchanged. Special consideration will be given to participants already in treatment.

In the event that a study change is recommended for participant safety reasons (including early stopping of inferior therapy), the PI acts to implement the change as expeditiously as possible to ensure safety of all participants on the study. In the unlikely situation that the PI does not concur with the DMC recommendation, then the Vice President for Research Administration must be informed of the recommendation of the DMC and of the PI's reason for disagreeing with the recommendation. The Vice President for Research Administration and the PI, in consultation with the DMC Chair, are responsible for reaching a mutually acceptable decision about the study. Confidentiality is maintained during these discussions. In the event that a change in a study is recommended for reasons other than participant safety (e.g., to extend accrual because of a lower than expected accrual rate), the DMC provides to the PI as much rationale for the proposed change as can be made without jeopardizing the conduct of the study. The PI is responsible for having an amendment prepared and submitted to the IRB the recommendations of the DMC and providing the rationale for the changes. IRB approval of the amendment will be required prior to implementation of the change, although a decision to override the DMC's recommendation is made only in the most exceptional circumstances.

All documents, investigative reports or information and conversations relating to this committee's work are strictly confidential and are not shared with anyone other than

other committee members. Although committee documents are subject to legal privileges as set forth in statutory and case law and are not subject to discovery during a litigation process, the privilege may be lost if committee documents are given to, shown to or discussed with non-committee members without an official DMC request to do so.

No communication of the deliberations or recommendations of the committee, either written or oral, is made outside of the committee except as provided for in these policies and procedures. All DMC members or alternates will sign statements of confidentiality at the beginning of an appointment period. Outcome (efficacy) results are strictly confidential and are not divulged to non-members (excepting the PI and Associate Vice President for Clinical Investigations) until the recommendation to report the results are accepted and implemented.

Individuals invited to serve on the DMC disclose to the Group Chair any potential, real or perceived, conflicts of interest. These include professional interest, proprietary interest and miscellaneous interest considerations. Potential conflicts that develop during the conduct of a trial should also be disclosed to the PI.

COMPLIANCE WITH REQUIREMENTS REGARDING THE REPORTING OF ADVERSE EXPERIENCES

Given the non-invasive, minimal risk nature of the proposed research, we anticipate that the types of adverse experiences that may occur, if any, will focus on concerns about possible distress associated with sensitive issues arising during data collection. The study includes procedures to minimize these risks.

Adverse Experiences Requiring Immediate Reporting**:** Two types of Adverse Experiences require prompt reporting to the IRB and the study sponsor: Serious Adverse Experiences and Unexpected Adverse Experiences. For serious or unexpected AEs, a written report is submitted to the Office of Protocol Research (OPR) within 10 working days of the adverse experience. Unexpected fatal or life-threatening experiences are phoned immediately to the OPR and the OPR will notify the appropriate sponsors within 3 days. For AEs that are not serious or not unexpected, written reports are submitted to OPR every month. Serious Adverse Experiences: For the majority of trials performed at MDACC, a serious adverse experience is a clinical event occurring subsequent to the administration of an agent or intervention which can be characterized as fatal, life-threatening, permanently disabling, requiring hospitalization, or an overdose.

Unexpected Adverse Experience: An unexpected adverse experience is a clinical event that is not identified in nature, severity, or frequency in the investigator's brochure, protocol, or other pertinent supporting literature. At times, the occurrence of an unexpected adverse experience might not be suspected until more than one event has occurred. Once the clinical event has been identified, all cases should be reported. No degree of unexpected toxicity is specified, but practically, it is unusual to be able to discern < grade 2 toxicity.

Adverse Experiences Associated with Participating in the Intervention: Dexamethasone may cause irregular heartbeat, slow heartbeat, sudden stopping of the heartbeat, enlarged heart muscle, heart failure, circulatory system failure, build-up of fluid, often in the legs or arms, high blood pressure , tearing of the walls of the heart, fainting, blood clots, inflammation in blood vessels (possible fever and/or fatigue), depression, unstable emotions, euphoria (abnormal feelings of great happiness, well-being), headache, increased pressure between the skull

and brain, difficulty sleeping, weakness, mood swings, inflammation of a nerve, personality changes, psychotic disorders, seizures, dizziness, acne, allergic skin inflammation, hair loss, tissue swelling, bruising, dry skin, abnormal skin redness, lightening and/or darkening of the skin.

Dexamethasone may cause fragile skin, increased hair growth, excessive body hair, anal itching, red or purple spots under the skin, skin rash, thinning of the skin, skin tests (such as for TB) may not be accurate, stretch marks, hives, decreased function of the adrenal glands (which produce hormones to regulate stress response), decrease in carbohydrate tolerance , Cushing's syndrome (possible obesity), diabetes, stunted growth in children, bleeding in the stomach/intestines area, enlarged abdomen , increased appetite, hole in the stomach and/or intestines, which may cause the contents to leak, nausea, inflammation of the pancreas (possible abdominal pain), sore in the stomach or small intestine, inflammation of the esophagus with sores, weight gain, enlarged liver, inflammation of the veins, fluid in the lungs (possible shortness of breath)

Dexamethasone may cause abnormal liver tests (possible liver damage), joint disease, death of bone tissue, increased risk of broken bone , loss of muscle mass , muscle disease that causes weakness, pain or weakness from damage to parts of the nervous system, decreased bone density, tickling and/or tingling sensation, rip in a tendon , broken bones in the spine , weakness, cataracts (clouding of the lens of the eye), bulging eye, increased pressure in the eye (possible loss of vision), increased sugar in the urine (possible liver disease), abnormal build-up of fat in the back of the neck, severe allergic reaction, loss of blood supply to the bones, excessive sweating, hiccups, problems with wound healing , infection, malignant skin lesions, moon face, new occurrence of cancerIn addition to the monitoring that is conducted by the M. D. Anderson DMC, patients are closely followed by the staff of the project. Patients will be provided the telephone number of the PI and the research nurse in case they feel they need to reach someone immediately.

**Adverse Experiences Associated with Self-Report Questionnaires:** This study will involve the use of questionnaires and interviews that could reveal sensitive information (e.g., assessment of mood or other psychiatric disturbance). Procedures are in place to protect participant confidentiality. Such instruments are administered only by trained staff and after careful explanation to the participants about their purpose and use in this study. The instruments are not used to communicate psychiatric diagnosis to the participant. However, the PI or one of the co-investigators reviews the results and if in their clinical judgment the results reveal a degree of disturbance that requires further professional consultation, the participant is contacted. Possible outcomes of this contact include referral to the participant's primary care physician and/or other physician, and/or other mental health providers.

## ASSURING THAT ACTION RESULTING IN SUSPENSION OF TRIAL IS REPORTED TO ACS PROGRAM DIRECTOR RESPONSIBLE FOR THE GRANT

Any human subjects research that is not being conducted in compliance with applicable institutional policy and Good Clinical Practices will be suspended by the IRB. An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include the necessary and appropriate notifications of such actions to the institution's administration, funding agency, ACS other sponsor.

**DATA QUALITY AND INTEGRITY**

Because of the ongoing monitoring of the project, study investigators and staff are responsible for ensuring that data quality assurance procedures are developed and maintained. Several procedures will be used to maintain the integrity of the data. All databases will be stored in a centralized location on one of the departmental servers, which is backed up daily, with access limited to specific users at the discretion of the PI. The PI will assure that audits of selected subsets of data are performed and that appropriate safeguards of participant privacy are maintained. Privacy safeguards will include appropriate password protection and physical security for all computer systems. Patient names will not be stored in data files; records linking participants' names with the computer identifiers will be kept in a separate file and encrypted.

A relational database will be created in Microsoft ACCESS to store all project-related data. ACCESS can accommodate complex relationships among tables, allowing large quantities of data to be integrated into a single database. Relational databases such as ACCESS also allow for powerful and flexible queries and reports. ACCESS can be easily customized using Visual Basic for Applications (VBA) code, allowing the inclusion of many design features ideal for behavioral science research. These features include more user-friendly interfaces, the ability to specify valid ranges for variables, and double-entry systems for data, all of which help to maintain data integrity. We will use the built-in security features of ACCESS to restrict user access.

Additional quality assurance procedures include a data collection protocol documented in a protocol manual; a two-stage editing procedure for survey data collection consisting of the initial review of the data collection form by a project member immediately following data collection, and a second review by a project member who will record any significant deviations from the protocol; and regular meetings between the study statistician, the PI, data managers, and other project staff to review problems and solutions, and discuss concerns. Data entry systems, whether via scannable forms, or hand entry with verification, specifically provide field checks, range checks for continuous variables and valid value checks for categorical variables; checks for legitimate dates and times and logical consistency. A specific audit trail system that identifies the date, time, and individual making changes on the database will be part of the data-entry system. During data collection, we will either issue reports weekly or following any new data entry, depending on the needs of the project. Queries and reports will be provided to the study statistician and the PI.

**F. Relevance to the cancer problem**

Approximately 50% of patients diagnosed with cancer die of progressive disease. The overwhelming majority of patients develop devastating physical and psychosocial symptoms. Those symptoms decrease the quality of life of patients. Circulating cytokines and inflammatory proteins have been thought to be directly associated with pain, and cognitive impairment, depression, fatigue, cachexia, and sleep disorder. Steroids decreases the intensity of symptoms namely Fatigue, nausea, anorexia and pain that occur frequently in advanced cancer and one of the mechanisms it exerts such effects by decreasing a cytokines levels that mediate these symptoms. Despite widespread acceptance and frequency of steroid therapy in patients with cancer symptom management, the data is inadequate to draw definitive conclusions about the efficacy of these compounds in the management of pain and other symptoms. The role steroids on cancer related fatigue, pain, appetite and nausea (which are common symptoms in advanced cancer), their effects on cytokines need to be defined through

randomized controlled studies using updated and validated Symptom assessment tools and laboratory correlates (which were lacking in the previous studies on corticosteroids for symptoms). Our findings will also allow investigators 1) To effectively treat the symptoms clusters in advanced cancer patients and improve their quality of life. 2) Establish Cause and effect relationship between symptoms and cytokines. 3) To establish the use of dexamethasone for symptom control in advance cancer patients through randomized controlled studies using updated and validated Symptom assessment tools and laboratory correlates 4) Development of cytokine specific suppressive therapies that could be used to prevent and treat these troubling symptoms.

G**. Facilities**: MD Anderson Cancer Center and Lyndon Baines Johnson Hospital, Houston, TX

## REFERENCES

1. Paice J. Assessment of symptom clusters in people with cancer. Journal of the National Cancer Institute Monographs No. 32, 2004; 98-102
2. Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status patients with cancer. Onco Nurs Forum 2001; 28:465-70.
3. Trask PC, Griffith KA. The identification of empirically derived cancer patient subgroups using psychosocial variables. J of Psychosomatic Research 2004; 57: 287-295.
4. Cleeland CS, Pain and symptom burden: lessons from patients with cancer. Presentation at the American Pain Society Meeting. Baltimore, MD, March 14-17, 2002; American Pain Society, Glenview, IL.
5. Lee BN, Dantzer R, Langley K, Bennett G, Dougherty P, Dunn A, Meyers C, Miller A, Payne R, Reuben J, Wang X, Cleeland C. A Cytokine-based neuroimmunologic mechanism of cancer-related symptom. Neuroimmnomodulation 2004; 11:279-292.
6. Cleeland C, Bennett G, Dantzer R, Dougherty P, Dunn A, Meyer C, Miller A, Payne R, Reuben J, Wang X, Lee B. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. Cancer 2003; 97:2919-2925.
7. O'Brien S, Scott L, Dinan T. Cytokines: abnormalities in major depression and implications in pharmacological treatment. Hum Psychopharmacol 2004; 19(6): 397-403.
8. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. Lancet. 2003 Aug 23;362(9384):640-50.
9. Bruera E, Sweeney C. Cachexia and asthenia in cancer patients. Lancet Oncol. 2000 Nov; 1:138-47.
10. Haack M, Pollmacher T, Mullington J. Diurnal and sleep-wake dependent variations of soluble TNF- and IL-2 receptors in healthy volunteers. Brain, Behavior, and Immunity 2004; 18"361-367.
11. Ebrahimi B, Tucker S, Li D, Abbruzzese J, Kurzrock R. Cytokines in pancreatic carcinoma. Cancer 2004; Nov 3.
12. Pett S. Kelleher A. Cytokine therapies in HIV-1 infection: present and future. Expert Rev Anti Infect Ther 2003; 1(1):83-96

13. Bruera E, Roca E, Cedaro L et al. Action of oral methylprednisonlone in terminal cancer patients: A prospective randomized double blind study. Cancer Treat Rep 1985; 69:751-4.
14. Tannock IF, Osoba D, Stockler MR, *et al*. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996; 14:1756–1764.
15. Fainsinger RL, Spachynski K, Hanson J, Bruera E, Symptom control in terminally ill patients with bowel obstruction. J Pain Symptom Manage 1994;9:12-8.
16. Ettinger AB, Portenoy RK. The use of corticosteroids in the treatment of symptoms associated with cancer. J Pain Symptom Manage 1988;3:99–103
17. T. Popiela, R. Lucchi and F. Giongo, Methylprednisolone as palliative therapy for female terminal cancer patients. The Methylprednisolone Female Preterminal Cancer Study Group, *Eur J Cancer* **25** (1989) (12), pp. 1823–1829.
18. Della Cuna GR, Pellegrini A, Piazzi M. Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: a placebo-controlled, multicenter study. The Methylprednisolone Preterminal Cancer Study Group. Eur J Cancer Clin Oncol. 1989 Dec;25(12):1817-21.
19. R; Twycross, Corticosteroids in advanced cancer. BMJ 305:969-970.
20. Mercadante S, Fulfaro F, Casuccio A. The use of corticosteroids in home palliative care. Support Care Cancer 2001;9:386–389.
21. Vecht CJ, Hovestadt A, Verbiest HB, et al.: Dose–effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. Neurology 1994, 44:675–680.
22. Moertel C, Shutte A, Reitemeir R, et al. Corticosteroid therapy in preterminal gastro-intestinal cancer. Cancer. 1974;33:1607-1609.
23. Stiefel FC, Breitbart WS, Holland JC. Corticosteroids in cancer: neuropsychiatric complications. Cancer Invest. 1989;7:479-491.
24. Gralla RJ, Osoba D, Kris MG, et al., Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. American Society of Clinical Oncology. J Clin Oncol. 1999 Sep;17(9):2971-94.
25. J.P. Ioannidis, P.J. Hesketh and J. Lau, Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence, *J Clin Oncol* **18** (2000), pp. 3409–3422.
26. P. Kirkbride, A. Bezjak and J. Pater *et al.*, Dexamethasone for the prophylaxis of radiation-induced emesis: a National Cancer Institute of Canada Clinical Trials Group Phase III study, *J Clin Oncol* **18** (2000), pp. 1960–1966).
27. Inoue A, Yamada Y, Matsumura Y et al Randomized study of dexamethasone treatment for delayed emesis, anorexia and fatigue induced by irinotecan. Support Care Cancer. 2003 Aug;11(8):528-32. Epub 2003 Jul 03.

28. Bessler H, Mendel C, Straussberg R et al., Effects of dexamethasone on IL-1beta, IL-6, and TNF-alpha production by mononuclear cells of newborns and adults. Biol Neonate. 1999;75(4):225-33.
29. Rhodus NL, Cheng B, Myers S et al., A comparison of the pro-inflammatory, NF-kappaB-dependent cytokines: TNF-alpha, IL-1-alpha, IL-6, and IL-8 in different oral fluids from oral lichen planus patients. Clin Immunol. 2005 Mar;114(3):278-83.
30. El Azab SR, Rosseel PM, de Lange JJ, Dexamethasone decreases the pro- to anti-inflammatory cytokine ratio during cardiac surgery. Br J Anaesth. 2002 Apr;88(4):496-501.
31. Agarwal SK, Marshall GD Jr. Dexamethasone promotes type 2 cytokine production primarily through inhibition of type 1 cytokines. J Interferon Cytokine Res. 2001 Mar;21(3):147-55.
32. Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. Annu Rev Immunol 2002;20:125–63.
33. Odio CM, Faingezicht I, Paris M,et al., The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. N Engl J Med. 1991 May 30;324(22):1525-31.
34. Walsh D, Donnelly S, Rybicki L.The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. Support Care Cancer. 2000 May;8(3):175-90
35. Bruera E, DeLima L, Woodruff R, Doyle D. International Association for Hospice and Palliative Care (IAHPC): working to improve access to palliative care. Palliat Med 2004; 18(6): 491-3.
36. Argiles JM, Busquets S, Lopez-Soriano FJ. Cytokines in the pathogenesis of cancer cachexia. Curr Opin Clin Nutr Metab Care 2003; 6(4): 401-6.
37. Kurzrock R. The role of cytokines in cancer-related fatigue. Cancer 2001; 92(6):1684-1688.
38. Bruera E, Neumann C, Pituskin E, Calder K, Ball G, Hanson J. Thalidomide in patients with cachexia due to terminal cancer. Preliminary report. Ann Oncol. 1999; 10(7): 857-9.
39. Capuron L, Miller A. Cytokines and psychopathology: lessons from interferon alpha. Biol Psychiatry. 2004; 56:819-24.
40. Dantzer R, Wollman EE, Yirmiya R. Cytokines, Stress, and Depression. New York: Plenum, Kluwer Academic et al 1999.
41. Sephton SE, Sapolsky RM, Kraemer HC, Spiegel D. Diurnal cortisol rhythm as a predictor of breast cancer survival. J Natl Cancer Inst 2000;92:994–1000.
42. Kramer A, Yang FC, Snodgrass P, et al. Regulation of daily locomotor activity and sleep by hypothalamic EGF receptor signaling. Science 2001;294:2511–5.
43. Levi F. Circadian chronotherapy for human cancers. Lancet Oncol 2001;2:307–15
44. Greenberg DB, Gray JL, Mannix CM, Eisenthal S, Carey M. Treatment-related fatigue and serum interleukin-1 levels

in patients during external beam irradiation for prostate cancer. J Pain Symptom Manage. 1993; 8(4):196-200.
45. Sheng WS, Hu S, Lamkin A, Peterson PK, Chao CC: Susceptibility to immunologically mediated fatigue in C57BL/6 versus Balb/c mice. Clin Immunol Immunopathol. 1996; 81:161-167.
46. Davis JM, Weaver JA, Kohut ML, Colbert LH, Ghaffar A, Mayer EP. Immune system activation and fatigue during treadmill running: role of interferon. Med Sci Sports Exerc. 1998; 30:863-868.
47. Meyer CA, Valentine AD. Neurological and psychiatric adverse effects of immunological therapy. CNS Drugs 1995; 3:56-68.
48. Bruera E, Kim HN. Cancer pain. JAMA 2003 290(18): 2476-9.
49. Barnes EZ, Bruera E. Fatigue in patients with advanced cancer: a review. Int J Gynecol Cancer 2002; 12(5): 424-8.
50. Gupta S, Aggarwal S, See D, et al: Cytokine production by adherent and nonadherent mononuclear cells in chronic fatigue syndrome. J Psychiat Res, 31(1):149-156, 1997.
51. Cannon JG, Angel JB, Abad LW, et al: Interleukin-1$\beta$, Interleukin-1 receptor antagonist, and soluble Interleukin-1 receptor type II secretion in chronic fatigue syndrome: Journal of Clinical Immunology, 17(3) 253-261, 1997.
52. Cheney PR, Dorman SE, Bell DS: Letters and Corrections: Interleukin-2 and the chronic fatigue syndrome. Annals of Internal Medicine, 110(4): 321, 1989.
53. Moss RB, Mercandetti A, Vojdani A: TNF-$\alpha$ and chronic fatigue syndrome. Journal of Clinical Immunology, 19(5):314-316, 1999.
54. Sarna GP, Figlin RA, Pertcheck M, et al: Systemic administration of recombinant methionyl human interleukin-2 (Ala 125) to cancer patients: Clinical results. Journal of Biological Response Modifiers, 8:16-24, 1989.
55. Eskander ED, Harvey HA, Givant E, et al: Phase I study combining tumor necrosis factor with Interferon-$\alpha$ and Interleukin-2. Am J Clin Oncol, 20(5): 511-514, and 1997.
56. Vadhan-Raj S, Kudelka A, Garrison L, et al: Effects of interleukin-1 on carboplatin-induced thrombocytopenia in patients with recurrent ovarian cancer. J Clin Onc, 12:707-714, 1994.
57. Vehhuis G, Willemse P, Sleijfer D, et al: Toxicity and efficacy of escalating dosages of recombinant human interleukin-6 after chemotherapy in patients with breast cancer or non-small-cell lung cancer. J Clin Onc, 13:2585-2593, 1995.
58. Tepler I, Elias I, Smith JW, et al: A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. Blood, 87:3607-3614, 1996.
59. Rigas JR, Hoopes PJ, Meyer LA, et al: Fatigue linked to plasma cytokines in patients with lung cancer undergoing combined modality therapy. Proceedings of ASCO, 17:68a(Abstract 262), 1998.

60. Adler HL, McCurdy MA, Kattan MW, et al: Elevated levels of circulating interleukin-6 and transforming growth factor-β1 in patients with metastatic prostatic carcinoma. The Journal of Urology, 161:182-187, 1999.
61. Pusztai L, Mendoza TR, Reuben JM et al., Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. Cytokine. 2004 Feb 7;25(3):94-102.
62. Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorder of pain sensation like those seen in man. Pain 1988; 33:87-107.
63. Maier SF, Watkins LR. Immune-to-central nervous system communication and its role in modulating pain and cognition: Implications for cancer and cancer treatment. Brain., Behavior, and Immunity 2003; 17:S125-131.
64. Chacur M, Milligan ED, Gazda LS. Armstrong C, Wang H, Tracey KJ, Maier SF, Watkins LR. A new model of sciatic inflammatory neuritis (SIN): Induction of unilateral and bilateral mechanical allodynia following acute unilateral peri-sciatic immune activation in rats. Pain 2001; 94:231-244.
65. Milligan ED, Twining C, Chacur M, Wiesler-Frank J, Tracey KJ, Martin D. Poole S, Maier SF Watkins LR. Spinal glia and pro-inflammatory cytokines mediate “anatomically impossible” (mirror image) neuropathic pain. J Neusci. 2003; 23(3):1026-40.
66. Basu S, Sodhi A. Increased release of interleukin-1 and tumor necrosis factor by interleukin-2-induced lymphokine-activated killer cells in the presence of cisplatin and FK-565. Immunol Cell Biol 1992; 70:15-24.
67. Zaks-Zilberman M, Zaks TZ, Vogal SN. Induction of pro-inflammatory and chemokine genes by lipopolysaccharide and paclitaxel (Taxol) in murine and human breast cancer cell lines. Cytokine 2001; 15:156-165.
68. Aley KO, Reichling DB, Levine JD. Vincristine hyperalgesia in the rat: A model of painful vincristine neuropathy in humans. Neuroscience 1996; 73:259-265.
69. Galdiero M, Cipollaro DI, Folgore A, Cappello M, Giobbe A, Sasso FS. Effects of irradiation doses on alterations in cytokine release by monocytes and lymphocytes. J Med 1994;25:23-40.
70. Ibuki Y, Goto R. Contribution of inflammatory cytokine release to activation of resident peritoneal macrophages after in vivo low-dose gamma-irradiation. J RaDIAT Res 1999;40:253-262.
71. Peuckmann V, Fisch M, Bruera E. Potential novel uses of thalidomide: focus on palliative care. Drugs 2000; 60(2):273-92.
72. Billingsly KG, Alexander HR. The pathophysiology of cachexia in advanced cancer and AIDS. In: Bruera E, Higginson I, editors. Cachexia-anorexia in cancer patients. Oxford University Press, Oxford, UK, 1996:1-22.

73. Fong Y, Moldawer LL, Marano M, et al. Cachectin/TNF or IL-1 alpha induces cachexia with redistribution of body proteins. Am J Physiol 1989; 256: R659-65.
74. Leon LR, White AA, Kluger MJ. Role of IL-6 and TFN in thermoregulation and survival during sepsis in mice. Am J Physiol 1998; 275:R269-77.
75. Turrin N, Ilyin E, Gayle D, Plata-Salaman C, Ramos E, Laviano A, Das U, Inui A, Meguid M. Interleukin-1[beta] system in anorectic catabolic tumor-bearing rats. Curr Opin Clin Nutr Metab Care. 2004; 7:419-426.
76. Ramos EJ, Suzuki S, Marks D, Inui A, Asakawa A, Meguid MM. Cancer anorexia-cachexia syndrome: cytokines and neuropeptic. Curr Opin Clin Nutr Metab Care. 2004; 7(4):427-34.
77. Scheibel RS, Valentine AD, O'Brien S, Meyers CA. Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. J neuropsychiatry Clin Neurosci 2004; 16(2):185-191.
78. Erlanger DM, Kutner KC, Jacobs AR. Hormones and cognition: Current concepts and issues in neuropsychology. Neuropsychol Rev 1999; 9:175-207.
79. Chen G, Castro WL, Chow HH, Reichlin S. Clearance of 125 I-labeled interleukin-6 from brain into blood following intracerebroventricular injection in rats. Endocrinology 1997; 138:4830-4836.
80. Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP. Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-α Antagonist. J Clin Endocrinol Metab. 2004; 89(9):4409-4413.
81. Dinarello CA, Bunn PA. Fever. Semin Oncol 1997; 24(3): 288-98.
82. R. Alexanian, B. Barlogie and D. Dixon , High dose glucocorticoid treatment of resistant myeloma. *Ann Intern Med* 105 (1986) pp. 8–11.
83. De Weerdt O, van de Donk NW, Veth G, Bloem AC. Continuous low-dose cyclophosphamide-prednisone is effective and well tolerated in patients with advanced multiple myeloma. Neth J Med. 2001 Aug; 59(2): 50-6.
84. Leiguarda R, Sierra J, Pardal C, et al.: Effect of large doses of methylprednisolone on supratentorial intracranial tumors. A clinical and CAT scan evaluation. Eur Neurol 1985, 24:23–32.
85. Hatam A, Bergstrom M, Yu ZY, et al.: Effect of dexamethasone treatment on volume and contrast enhancement of intracranial neoplasms. J Comput Assist Tomogr 1983, 7:295–300.
86. Wang S, Lim G, Zeng Q, Sung B, Yang L, Mao J.Central glucocorticoid receptors modulate the expression and function of spinal NMDA receptors after peripheral nerve injury.J Neurosci. 2005 Jan 12;25(2):488-95.
87. Loblaw DA, Perry J, Chambers A, Laperriere NJ.Systematic review of the diagnosis and management of

malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group.J Clin Oncol. 2005 Mar 20;23(9):2028-37.

88. Devor M, Govrin-Lippmann R, Raber P in Corticosteroids suppress ectopic neural discharge originating in experimental neuromas. Pain. 1985 Jun;22(2):127-37.
89. Cella D, Davis K, Breitbart W, Curt G, for the Fatigue Coalition. Cancer-related fatigue: Prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol* 2001;19: 3385–91.
90. Curt GA, Breitbart W, Cella D. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000; 5(5):353-60.
91. Sweeney C, Neuenschwander H, Bruera . Fatigue & Asthenia in Doyle D, Hanks G, Cherny NI, Calman K (eds.). Oxford Textbook of Palliative Medicine. 2003; 8.4.4:560-568.
92. Miaskowski C, Portenoy R, Assessment and management of cancer related fatigue in Berger A, Portenoy R, Weissman D. (eds.). Principles and Practice of Palliative Care and Supportive Oncology. 2nd Ed. 2002; 141-153. Lippincott Williams& Wilkins. Philadelphia, PA.
93. Hardy JR, Rees E, Ling J, et al (2001) a prospective survey of the use of dexamethasone on a palliative care unit. Palliat Med 15:3-8.
94. Puccio M, Nathanson L. The cancer cachexia syndrome. *Semin Oncol* . 1997; 24: 277-287.
95. McEwen BS, Biron CA, Brunson KW, Bulloch K, Chambers WH, Dhabhar FS, Goldfarb RH, Kitson RP, Miller AH, Spencer RL, Weiss JM. The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. Brain Res Brain Res Rev 1997;23:79–133.
96. Demitrack MA, Crofford LJ. Evidence for and pathophysiologic implications of hypothalamic–pituitary–adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. Ann NY Acad Sci 1998;840:684–97.
97. Markman M, Sheidler V, Ettinger DS et al. Antiemetic efficacy of dexamethasone: randomized, double-blind, crossover study with prochlorperazine in patients receiving cancer chemotherapy. *N Engl J Med*. 1984; 311:549-52.
98. Cassileth PA, Lusk EJ, Torri S, DiNubile et al., Antiemetic efficacy of dexamethasone therapy in patients receiving cancer chemotherapy. Arch Int Med 1983;143:1347-9.
99. Aapro MS, Alberts DS. Dexamethasone as an antiemetic in patients treated with cisplatin. N Engl J Med. 1981 Aug 27;305(9):520.
100. Wilcox JC, Corr J, Shaw J, Richardson M et al. Prednisolone as a appetite stimulant in patients with cancer. Bri Med J 1984;288:27.

101. Plata- Salaman CR. Dexamethasone inhibits food intake suppression induced by low doses of interleukin-1 beta administered intracerebroventricularly. Brain Res Bull 1991: 27;737-8.

102. Weissman DE. Glucocorticoid treatment for brain metastases and epidural spinal cord compression: a review. J Clin Oncol 1988; 6:543-551.

103. Ferriera SH, Cunha FQ, Lorenzetti BB et al. Role of lipocortin in antihyperalgesic actions of Dexamethasone. Br J Pharmacol 1997; 231-239.

104. Mukaida N, Gussella GL, Kasahara T, et al., Molecular analysis of the inhibition of interleukin-8 production by dexamethasone in a human fibrosarcoma cell line. Immunology. 1992 Apr;75(4):674-9.

105. Petrovsky N, McNair P, Harrison LC. Diurnal rhythms of pro-inflammatory cytokines: regulation by plasma cortisol and therapeutic implications. Cytokine. 1998 Apr;10(4):307-12.

106. Bruera E, Belzile M, Pituskin E, Fainsinger R, Darke A, Harsanyi Z, Babul N, Ford I. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. J Clin Oncol. 1998; 16(10): 3222-9.

107. Watanabe S, Bruera E. Corticosteroids as adjuvant analgesics. J Pain Symptom Manage 1994;9(7):442-5.

108. Bruera E, Fainsinger R, MacEachern T, Hanson J. The use of methylphenidate in patients with incident cancer pain receiving regular opiates. A preliminary report. Pain. 1992; 50(1): 75-7.

109. Bruera E, Strasser F, Shen L, Palmer JL, Willey J, Driver LC, Burton AW. The effect of donepezil on sedation and other symptoms in patients receiving opioids for cancer pain: a pilot study. J Pain Symptom Manage 2003; 26(5): 1049-54.

110. Bruera E, Ernst S, Hagen N et al. Effectiveness of megestrol acetate in patients with advanced cancer: A randomized, double-blind, crossover study. Can Prev Contr 1998; 2:74-8.

111. Bruera E, Strasser F, Palmer JL, Willey J, Calder K, Amyotte G. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and

anorexia/cachexia: a double-blind, placebo-controlled study. J Clin Oncol. 2003; 21(1): 129-34.

112. Bruera E, Neumann C, Pituskin E, Calder K, Ball G, Hanson J. Thalidomide in patients with cachexia due to terminal cancer. Preliminary report. Ann Oncol. 1999; 10(7): 857-9.

113. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K, The Edmonton symptom assessment system (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991; 7(2): 6-9.

114. Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. Cancer 2000; 88:2164-2171.

115. Bruera E, Schoeller T, Wenk R, MacEachern T, Marcelino S, Hanson J, Suarez-Almazor M. A prospective multicenter assessment of the Edmonton staging system for cancer pain. J Pain Symptom Manage 1995; 10(5): 348-55.

116. Kaasa T, Loomis J, Gills K, Bruera E, Hanson J. The Edmonton Functional Assessment Tool: Preliminary development and evaluation for use in palliative care. J Pain Symptom Manage 1997;13(1):10-19.

117. Strasser F, Sweeney C, Willey J, Benisch-Tolley S, Palmer JL, Bruera E. Impact of a half multidisciplinary symptom control and palliative care outpatient clinic in a comprehensive cancer center on recommendations, symptom intensity, and patient satisfaction: a retrospective descriptive study. J Pain Symptom Manage 2004; 27(6):481-91.

118. Elsayem A, Swint K, Fisch M, Palmer JL, Reddy S, Walker P, Zhukovsky D, Knight P, Bruera E. Palliative care inpatient service in a comprehensive cancer center: clinical and financial outcomes. J Clin Oncol 2004; 22(10): 2008-14.

119. Jenkins CA, Schulz M, Hanson J, Bruera E. Demographic, symptom, and medication profiles of cancer patients seen by the palliative care consult team in a tertiary referral hospital. J Pain Symptom Manage 2000;19(3):174-84.

120. Bruera, E, Neumann, CM. Respective limits of palliative care and oncology in the supportive care of cancer patients. Support Care Cancer 1999; 7:321.

121. Vadhan-Raj S, Broxmeyer HE, Hittelman WN, et al. Abrogating chemotherapy-induced myelosuppression by recombinant granulocyte-macrophage colony-stimulating factor in patients with sarcoma: Protection at the progenitor cell level. Journal of Clinical Oncology, Vol 10(8):1266-1277, 1992.

122. Hamilton RF Jr., Vadhan-Raj S, Uthman M, et al. The in vivo effects of PIXY321 therapy on human

monocyte activity. Journal of Leukocyte Biology, 53:640-650, 1993.

123. Perkins RC, Vadhan-Raj S, Scheule RK, et al. Effects of continuous high dose rhGM-CSF infusion on human monocyte activity. American Journal of Hematology, 43:279-285, 1993.

124. Lee AM, Vadhan-Raj S, Hamilton RF Jr., et al. The in vivo effects of rhIL-1$\alpha$ therapy on human monocyte activity. Journal of Leukocyte Biology, 54:314-321, 1993.

125. Cella D. Manual of the Functional Assessment of Chronic illness Therapy (FACIT) Measurement System. Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University. Version 4, 1997.

126. Daut, R.L., Cleeland, C.S. & Flanery, R.C. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other disease. Pain. 1983; 17:197-210.

127. Cleeland, C.S. Measurement of pain by subjective report. In C.R. Chapman & J.D. Loeser (Eds.), Advances in Pain Research and Therapy, Vol 12: Issues in Pain Measurement. 1989; p.391-403. New York: Raven Press.

128. Arsuaga E, Higgins J, Sifre P. Separation of brain-damaged from psychiatric patients with the combined use of an ability and a personality test: a validation study with a Puerto Rican population. J Clin Psychol. 1986; 42(2): 328-31.

129. Johnston M, Pollard B, Hennessey P. Construct validation of the hospital anxiety and depression scale with clinical populations. J Psychosomatic Res. 2000; 48:579-584.

130. Redelmeier D, Guyatt G, Goldstein R. Assessing the minimal important difference in symptoms: a comparison of two techniques. J Clin Epidemiol 1996; 49:1215-1219.

131. Guyatt G, Feeny D, Patric D. Measuring health-related quality of life. Annals of Internal Medicine. 1993; 118:622-629.

132. Palmer JL. Analysis of missing data in palliative care studies. Journal of Pain and Symptom Management, 28 (6), 612-618, 2004.

## LETTERS OF RECOMMENDATION

List the name, title, and address of the three individuals whose letters of recommendation have been requested. Each letter of recommendation must be in a sealed envelope and attached to the cover page of the original copy of the application with a paper clip.

## PART II

**FACULTY OR SCIENTIFIC APPOINTMENT (of candidate):**

**PROGRAM GOALS AND PROPOSED TRAINING:**

**INSTITUTIONAL RESOURCES AND ENVIRONMENT:**

**TRAINING EXPERIENCE OF MENTOR (S)**

| **ABBREVIATED CURRICULUM VITAE OF MENTOR (S)**<br>*(Do not exceed two pages for total biographical information.)* | | |
|---|---|---|
| Last name, first name | | |
| Major research interest: | | |
| **Education** | | |
| Institution/Location | Degree/Year Conferred | Field of Study |
| | | |

| **Appointments** |
| --- |
| **Publications** |

**SUPPORT OF MENTOR (S)**
(Current and Pending)

Give source of support, identifying number, project title, name of principal investigator, percent effort of each professional named (including collaborators but not consultants), dates of entire project period, and direct costs for the entire period and for the current year.