Protocol Title: Effects of Physical Activity Plus Short Course of Dexamethasone for Cancer-Related Fatigue in Advanced Cancer

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A. OBJECTIVES:

Primary Objectives:
1. To determine the feasibility, adherence, and satisfaction with Physical Activity (PA) plus Dexamethasone (PA+ DEX).
1.1. PA+ DEX will be feasible as evidenced by adherence rate to daily use of PA+ DEX will be ≥75%.
1.2. More than 75% of patients will indicate satisfaction with the PA+ DEX as somewhat satisfied or completely satisfied.

Secondary Objectives:
2. To explore the preliminary efficacy of PA+ Hi Dex group (PA for 4 weeks plus high dose dexamethasone for 1 week) and PA+ Lo Dex groups (PA for 4 weeks plus low dose dexamethasone for 1 week) on CRF as measured by FACIT-F at the end of one week
2.1. PA+ Hi Dex will result in robust reduction in FACIT-F subscale scores (≥10 point improvement in 60%of patients)
3. To explore the effects of PA+ Hi Dex on the various dimensions of CRF [PROMIS-F], i.e., affective/emotional (Hospital Anxiety Depression Scale[HADS]); physical/behavioral (The Multidimensional Fatigue Symptom Inventory-Short Form[MFSI-SF], Pittsburg Sleep Quality Index), physical activity and function (30 second sit-to stand test, Six minute walk test) before and after treatment.
3.1. By targeting the various associated factors of CRF including subjective measures (such as anxiety, depression, and sleep disturbance) and objective measures, PA+ Hi Dex improves CRF.

B. BACKGROUND / RATIONALE:

Cancer-related fatigue (CRF) is the most frequently reported symptom associated with cancer and its treatment. CRF is more severe and debilitating in patients with advanced cancer than in those with early cancer or in cancer survivors.[1-4] Its frequency ranges from 60% to 90% in patients who are receiving palliative care.[4,5] As a result of improved therapy, patients with advanced cancer are living longer, and due to advances in treatment for pain and nausea, clinicians are more frequently recognizing CRF as an important symptom that negatively affects quality of life (QOL), interferes with daily activity, has potentially devastating social and economic consequences, and affects the ability to receive palliative cancer therapy.[6] However, only a few studies have been conducted to determine whether established therapies for CRF such as physical activity are effective in palliative care patients.[3,7,8] In addition, prior pharmacological studies for CRF in palliative care have shown mixed results.[1,7,9] Given the high frequency and adverse effects of CRF and the limited treatment options in advanced cancer patients, further research on new treatment strategies is greatly needed. Preliminary data from our group[10] and others[7,10-15] have shown that corticosteroids are able to improve CRF and related symptoms in patients with advanced cancer. In a recent study of 84 evaluable patients, oral dexamethasone (Dex) at a standard dose of 8 mg daily was associated with significant improvement in CRF.[16] There were no significant differences in the adverse effects between patients who received Dex and placebo (41/62 vs. 44/58; p=0.14). However, despite improvement, patients still had persistent CRF (56% responded to Dex with significant improvement in CRF, whereas 44% had minimal or no improvement). In cancer patients receiving treatment and in cancer survivors, physical activity has been shown to improve CRF.[16-19] Randomized clinical trials among cancer patients who participated in an physical activity program showed significant increases in cardiovascular capacity, improved overall health-related QOL, less fatigue, fewer sleeping

problems, and increased self-reported physical functioning, general well-being, self-esteem, and energy.[17,18] A recent Cochrane meta-analysis[18] of 28 clinical trials that included more than 2000 cancer patients confirmed these findings. However, the evidence suggests that physical activity has a very modest benefit (effect size 0.23) in improving CRF.[19] This lack of robust response (defined as ≥10 points on the Functional Assessment of Cancer Illness Therapy-Fatigue (FACIT-F) subscale)[20] to these treatments may be due to a lack of effect on the multidimensional and multifactorial nature of CRF.[21] Hence there is a need to test combined therapies for CRF such as higher doses of Dex with physical activity intervention, since these treatments individually target the multidimensional causative factors contributing to CRF in advanced cancer. Our long-term goal is to reduce CRF and thereby improve QOL in patients with advanced cancer. The objective of the proposed study is to evaluate the effects of *PA+ Hi Dex* for the treatment of CRF in patients with advanced cancer.

Rationale to conduct this study:
Cancer-related fatigue (CRF) is more severe and debilitating in patients with advanced cancer than in those with early cancer or in survivors. In advanced cancer patients receiving palliative care, moderate to severe fatigue is associated with poor quality of life outcomes, performance status scores, frailty and poor overall survival. Only a few studies have been conducted to determine whether established therapies for CRF such as physical activity (PA) are effective in palliative care patients. Even in early cancer and survivors patients the overall clinical effectiveness of PA is low to moderate (Effect size ~0.28). In advanced cancer patients another barrier to PA is adherence to the initiation and adherence. In addition, prior pharmacological studies for CRF in palliative care have shown mixed results.

Prior study using low dose dexamethasone 4mg orally twice daily was associated with significant improvement of fatigue at Day 8 in dexamethasone arm [8.01 (7.81)] compared to placebo arm [3.06(7.28)], p=0.005 but the numbers of adverse effects did not significantly differ between the groups at 2 weeks and at the end of open label phase (17/62 vs. 11/58, P=0.14; and 20/42 vs 18/47, P=0.37). Despite improvement, patients still had persistent CRF (56% responded to Dexamethasone with significant improvement in CRF, whereas 44% had minimal or no improvement). The low dose dexamethasone 4mg orally twice a day used in our previous study will be our control group and will be used to compare dexamethasone 8mg orally twice along with physical activity to evaluate from the perspective of feasibility, efficacy, and toxicity it will be also help us to define the effect size for a large randomized controlled study.

The overall hypothesis of this project is that the use of the combination of dexamethasone plus PA is feasible and high dose dexamethasone with PA would provide more robust improvement of cancer related fatigue in 60% of patients due to the anti-inflammatory effect, improvement in symptoms distress improvement overall well-being and this would enable the patient in initiation and adherence to the PA intervention and thereby engage and sustain PA over the period of 4 weeks. We also anticipate the study will be safe and feasible and this based on the data from previous studies in which 341 advanced cancer patients received similar dose of dexamethasone or equivalent as will be used in this study of dexamethasone. In addition, measures such as excluding patients with history of falls, infections, monitoring the blood glucose and performing the sit and stand test will ensure safety in terms of hyperglycemia and myopathy.

Significance: The proposed research is significant because it will be the first to test the effects of the combined interventions of Dexamethasone and physical activity in advanced cancer patients, a group that is living longer as more treatments are available yet experience the most severe levels of CRF among cancer patients because of the lack of effective treatment options.[10,11] As preliminary studies[12-15] indicate, we anticipate that this combination therapy, if effective, will provide more robust and clinically effective improvement of CRF,[16] which would facilitate patients continuing cancer therapy since it would be tolerated and effective in controlling disease. This study will provide important evidence to show the joint effects of Dexamethasone and physical activity in improving CRF. Other important benefits of this study are that it will provide important data on the role of combination intervention in other QOL measures such as anxiety,

depression, and the role of combination interventions on objective measures of physical activity, strength, and pro-inflammatory cytokines.

C. Preliminary Studies:

Pharmacologic Treatment of Fatigue: Our team's studies in patients with advanced cancer allowed us to establish the high frequency, severity and multidimensional nature of fatigue.[12,14,15,17-24] We conducted studies of various assessment methods for fatigue and were able characterize fatigue in this patient population.[24-28] In a preliminary study of 31 advanced cancer patients, we found that methylprednisolone (MP) 32mg/day significantly improved CRF ($p<0.01$) compared with placebo with no significant differences in side-effects between groups.[14] As shown in Table 1, this study was unable to detect sustained responses to Day 33 perhaps due to low doses, type of the steroid, and lack of validated tools. In a recently published[15] RCT study of 84 patients with advanced cancer, oral Dexamethasone at 8 mg/day for 14 days was found to be effective in alleviating CRF compared with placebo. The mean improvement in the FACIT-F subscale was significantly higher in the Dexamethasone group than in the placebo at Day 8 in dexamethasone arm [8.01 (7.81)] compared to placebo arm [3.06(7.28)], p=0.005 as well as Day 15(9 [10.3] vs. 3.1 [9.59], P=0.008).[15] When both the groups received Dexamethasone for 14 more days on an open-label basis (Day15-29), the effect of Dexamethasone was not sustained in the Dexamethasone compared with the placebo group (0.67 [9.4] vs. 6.86 [13]; P=0.044) [fig. 2]. However, the numbers of adverse effects did not significantly differ between the groups at Day 15 (primary end point) and at the end of open label phase (17/62 vs. 11/58, P=0.14; and 20/42 vs 18/47, P=0.37). Based on the preliminary data, we conclude that 8 mg/d of Dexamethasone is safe if administered for 7 days as proposed in this study; however, the improvement of CRF was not robust enough for sustained clinical benefit. Hence, we hypothesize that the joint effects of a ***PA+ Hi Dex*** would result in a robust response (defined as change of ≥10 points on FACIT-F scores[16]).

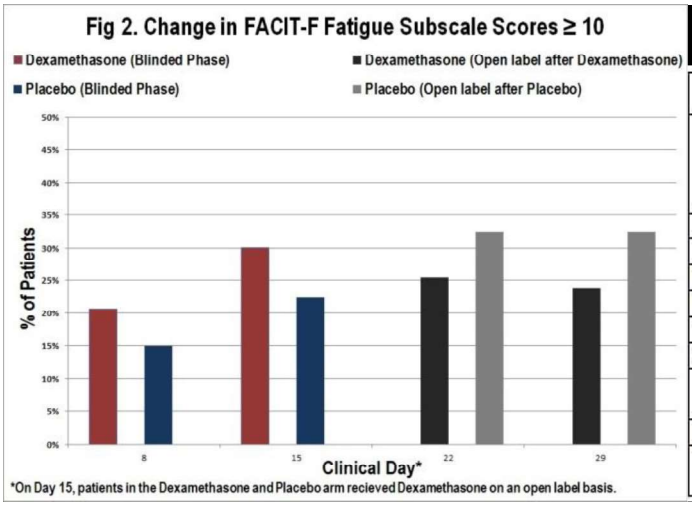


Table 1 – Effects of Methylprednisolone (MP) on the clinical parameters*

	Performance Status (ECOG)	Activity Score	Appetite (visual analogue, 0-100)
Baseline	3.5 ± 0.7	3.2 ± 2	26.5 ± 10
Placebo	3.2 ± 0.6	3.4 ± 2	29.5 ± 15
MP (Days5-13)	3 ± .08	6.7 ± 2.4	40.1 ± 15
MP (Day 33)	3.3 ± 0.8	4 ± 2	33 ± 13
P values			
Baseline vs placebo	NS‡	NS‡	NS†
Placebo vs MP (Days 5-13)	NS	< 0.01	< 0.05
Placebo vs MP (Day 33)	NS	NS	NS

*Unless otherwise specified, values vs mean ± SD. NS vs not significant.

Table 2. Corticosteroids (dosage and duration) in the management of cancer related symptoms					
Author	**Number of patients**	**Treatment Duration (days)**	**Study Drug***	**Equivalent Dexamethasone daily dose (mg)**	**Primary Outcome for the study**
Moertal et al. 1974[15]	116	14	Dex	0.75-1.5	Cancer related symptoms including low appetite, strength, and overall survival
Willox et al. 1984[26]	41	14	PS	2.25	Poor appetite
Bruera et al 1985[43]**	40	14	MP	6	Combination of pain, tiredness, anorexia and depression
Della Cuna 1989[14]**	**40**	**56**	**MP**	**23**	Quality of life
Popiela et al 1989[13]**	**173**	**56**	**MP**	**23**	Quality of life
Loprinzi et al 1999[12]**	455	30	Dex	3	Low appetite
Hardy et al 2001[25]	**160**	**22**	**Dex**	**12**	Anorexia, nausea, low mood, pain and vomiting.
Mercadante et al 2001[11]	**376**	**26**	**Dex, MP**	**4-16**	Cancer related symptoms including anorexia, fatigue, dyspnea, headache and drowsiness
Bruera et al 2004[37]**	**51**	**7**	**Dex**	**20**	Chronic nausea
Yennurajalingam et al 2013[16]**	84	14	Dex	8	fatigue
Paulsen et al 2014[70]**	50	7	MP	8	pain
***MP= Methylprednisolone, Dex=Dexamethasone, PS=Prednisolone** ****Randomized, double blind placebo controlled studies**					

Prior studies conducted in palliative patients by our team and others used various doses of steriods (Table 2). In the 341 patients who received more than 16 mg /day or equivalent dose of dexamethasone for 7 days there was no report of significant toxicity due to hyperglycemia and myopathy.

Physical activity: Prior studies led by Dr. Basen-Engquist (Co-I) tested intervention in patients with highly symptomatic prostate cancer (TPRB-98-103-01-PBP)[29] and in breast cancer (CA89519).[30] The breast cancer study improved 6-minute walk performance and QOL.[30] In an R01-funded study of physical activity in endometrial cancer survivors,[31] the intervention completed a high percentage and was well received among the participants. The same methods will be used in the proposed study.

Table 3 Preliminary data of adherence and safety of exercise and attention control exercise patients on an ongoing multimodal fatigue study (NCT01410942)

Pt. no	% calls completed	Goals met week 2	Goals met week 3	Goals met week 4	Goals met week 5	Goals met week 6	Exercise side effects
1	100%	yes	yes	yes	yes	yes	none
2	100%	yes	yes	no/ foot pain	yes	yes	none
3	100%	no/back pain	no/back pain	no/epidural back	no	yes	none from exercise
4	100%	yes	yes	no/fatigue	yes	yes	none
5	100%	yes	no/no time	no/no reason	yes	yes	none
6	100%	no/soreness	no/no time	no/fatigue	no	no/fatigue	soreness
7	40%	no	no answer	no answer	no answer	yes	none
8	100%	no	no/no time	yes	no	no/shoulder pain	yes/shoulder pain
9	80%	no/fatigue	no	no/no time	no answer	no	none
10	60%	yes	no/fatigue	no/no time	w/d	w/d	none
11	withdrew						
12	80%	no/fatigue	yes	no/fatigue	no answer	yes	fatigue

An ongoing study in highly symptomatic prostate cancer patients, NCT01410942, conducted by the same team as that in the proposed study (PI: Yennu), uses the same standardized physical activity regimen in combination with study drug. Table 3 shows the completion rates adherence and safety data of the first 12 patients enrolled (blinded). The enrolled patients in this ongoing study had no difficulty in completing all the assessments. Based on the preliminary data presented, we conclude that this proposed physical activity would be feasible and safe.

Inflammatory cytokine studies: Prior studies[32-35] by our group showed wide variability in serum cytokine levels in patients with advanced cancer and hence the need to assess cytokines levels in LPS activated monocytes. Physical activity results in modulation of TNF-α, IL-1b, and IL-6,[36] interleukin-1 receptor antagonist (IL-1RA), TNF-receptors (TNF-R), and IL-10 levels.[37] Figure 4 shows the synthesis of TNF-a by LPS-activated monocytes isolated from patients at baseline (D0) and at weeks 1- 5 after treatment with Dexamethasone (Dex). In patients treated with 8 mg Dex daily (dark histograms), the percentage of LPS-activated monocytes that synthesized TNF-α decreased, whereas in patients receiving placebo (light histograms) for the first 2 weeks there was no change in the percentage of LPS-activated monocytes that synthesized TNF-α from D0 until week 2. Thereafter, when placebo patients (light histograms) switched to open-label Dex, there was a decrease in the percentage of LPS-activated monocytes that synthesized TNF-a. We will be collecting optional blood for future research which may include this cytokine analysis.

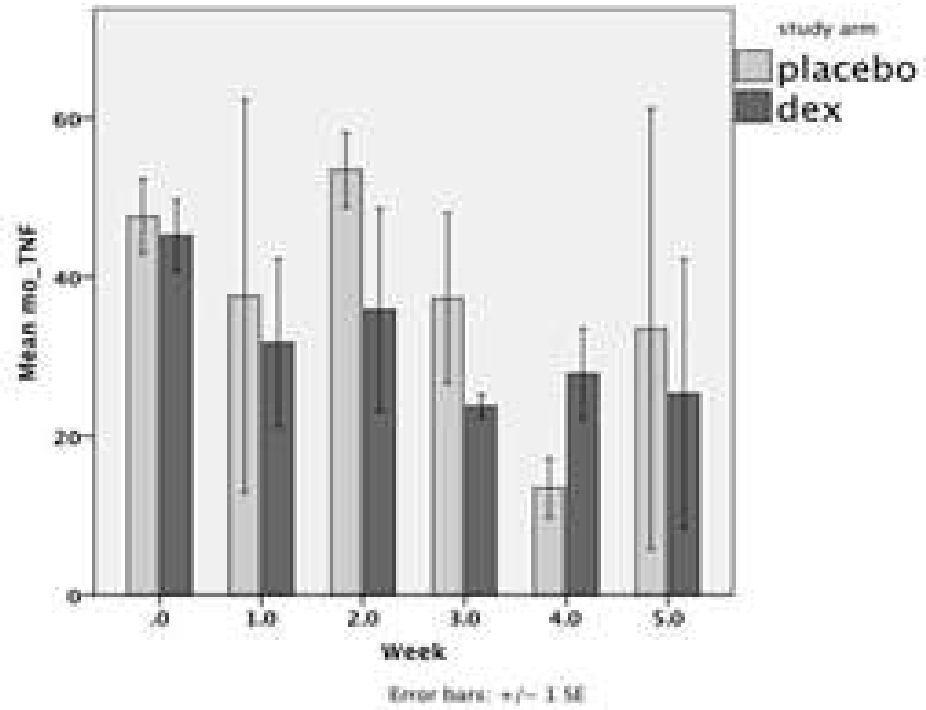


Fig. 3. Change in TNF-α production by LPS-activated monocytes from dexamethasone-treated patients and placebo-treated patients in double-blind phase (Days 8 and 15) and in dexamethasone-only open-label phase (Days 29 and 35).

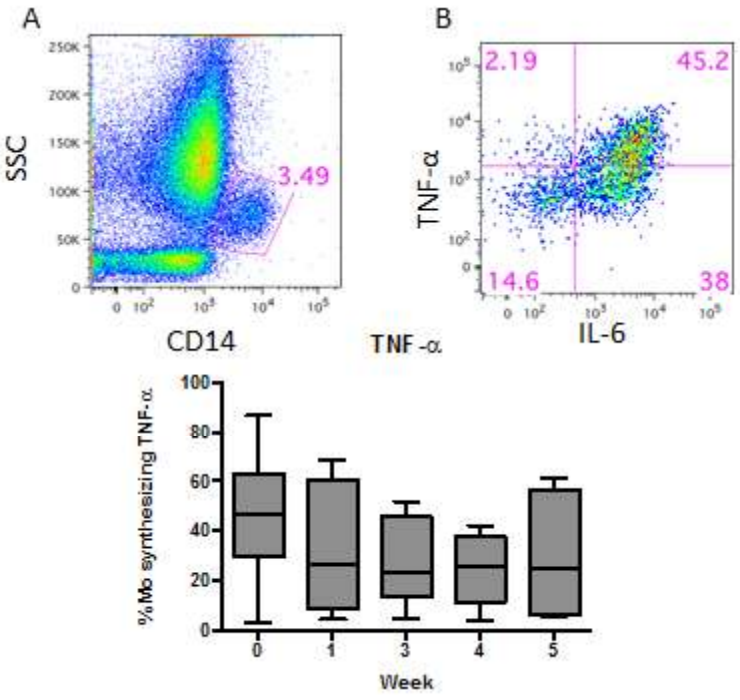


Figure 4. Monocyte Phenotype and LPS-induced cytokine synthesis. (A) Monocytes are enumerated in whole blood as $CD14^{+}SSC^{mid}$ cells. (B) After a 4 hour incubation with LPS, the percentage of cell synthesizing cytokines can be enumerated. C) TNF-α synthesis by monocytes decreases in patients treated with 8mg dexamethasone daily.

D. RESEARCH DESIGN AND METHODS

D1.

Eligibility Criteria:

Inclusion criteria:

- **(A)** A diagnosis of advanced cancer (defined as metastatic or recurrent) with fatigue ≥4/10 (0-10 scale) on the Edmonton Symptom Assessment Scale (ESAS)
- **(B)** The presence of fatigue for at least 2 weeks;
- **(C)** Normal cognition;
- **(D)** Hemoglobin >8 g/L within 1 week of enrollment in the study; and a life expectancy of ≥4 months.
- **(E)** No evidence of significant anxiety or depression as determined by a total HADS scores of <21;
- **(F)** Definition of advanced cancer includes those patients who have metastatic or refractory disease according to their treating oncologist
- **(G)** Patients must be able to understand, read, write, and speak English or Spanish.

Exclusion criteria:

a) Patients with history of hypersensitivity to dexamethasone or having any contraindication to physical activity as determined by the treating physician;
b) Reports a fall in the past 30 days;
c) Uncontrolled diabetes mellitus as defined by a random blood sugar of >200mg/dl not being monitored by their primary care physician
d) Sepsis and/or acute, chronic, or ongoing infections that are currently being treated with systemic antimicrobials
e) We will exclude patients with current, active Peptic ulcer disease,
f) Neutropenia as defined by an absolute neutrophil count (ANC) of < 1000 cells/mm
g) Regular participation in moderate- or vigorous-intensity physical activity for ≥30 minutes at least 5 times a week and strength training for ≥2 days;
h) Severe cardiac disease (New York Heart Association functional class III or IV) or coronary artery disease.

Rationale for Various Tumor Types:

(1) CRF is a syndrome that results from increased production of inflammatory cytokines and tumor by-products. This pathophysiology is more related to the interaction between cancer and the host rather than to any specific histology, as demonstrated by similar rates of frequency and severity of fatigue across various tumor types in patients with advanced cancer.[22,24]
(2) The frequency, severity, and mechanisms of CRF in patients with advanced cancer who have various tumor types are largely the same, on the basis of clinical trials of methylphenidate,[42] donepezil,[14] and fish oil[40] in the treatment of CRF by our group and according to studies by other groups.
(3) By including patients with various tumor types, we will obtain a more representative distribution in terms of age, sex, and behavior than we would in a study of patients with a single tumor type.
(4) Despite the type of cancer that patients have, those with advanced cancer who are undergoing treatment for CRF, rate CRF as the most significant of all symptoms that affect their QOL. Our ultimate goal is to reduce

these symptoms in this distressed cohort/population. Eligible patients with complete the study assessments (as detailed in Table 2).

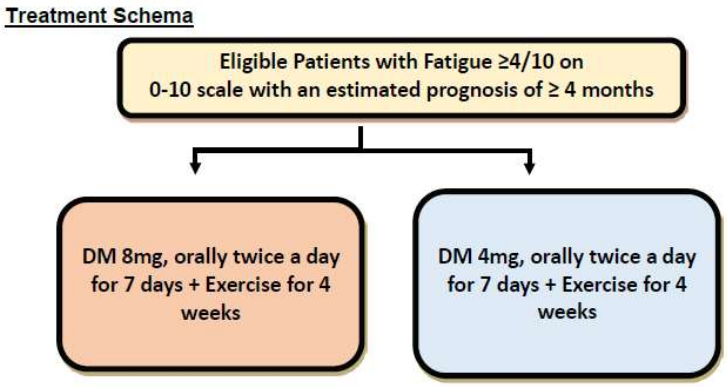
Patient Recruitment: 70 patients will be recruited from outpatient centers of palliative care, pain, and oncology at the MD Anderson Cancer Center, Houston, Texas.

For this study, we will use a randomized double-blind design. Seventy patients will be randomized equally between the 2 treatment arms. The randomized assignment will be obtained via the Department of Biostatistics, Clinical Trial Conduct Website.

D2. Treatment Plan:
Potential study subjects will be asked for verbal consent prior to completing the HADS to determine eligibility.

Patients who are eligible and interested in participating will be asked to give written consent and then randomized into 1 of the 2 arms of the study. The length of dexamethasone treatment is 7 days. Patients will complete the assessments as shown in Table 4. PI will obtain approval from patient's primary oncologist in all cases prior to study enrollment.

Figure 5



The research nurse/coordinator will conduct all baseline assessments and follow-up as shown Table 2. The pharmacological treatment assigned to individual patients will be known to only the statistician and the investigational pharmacy. The research nurse will then provide instructions and prescriptions for the study medication. The research nurse/coordinator will then perform scheduled assessment as per Table 2.

Rationale for use of one week of dexamethasone and four weeks of physical activity intervention.
In cancer patients receiving treatment, physical activity (PA) has been shown to improve CRF (Cramp F 2012). Randomized clinical trials among cancer patients who participated in an PA showed significant increases in cardiovascular capacity; improved overall health-related QOL; less fatigue; fewer sleeping problems; and increased self-reported physical functioning, general well-being, self-esteem, and energy [41,42]. A recent Cochrane meta-analysis (Cramp F 2012) of 28 clinical trials that included more than 2,000 cancer patients confirmed these findings. However, the evidence suggests that physical activity has a very modest benefit (effect size 0.23) in improving CRF [13]. Also PA is a universal prescription given to patients at our supportive care center. The low effect size regards to benefit of physical activity is due to low adherence.
We therefore hypothesize that the use of high dose dexamethasone for 7 days would provide more robust improvement of cancer related fatigue in 60% of patients due to the anti-inflammatory effect, improvement in symptoms distress improvement overall well-being and this would enable the patient in initiation and adherence to the PA intervention and thereby engage and sustain PA over the period of 4 weeks.

Objective #1: To determine the feasibility, adherence, and satisfaction with *PA+ Dexamethasone*.

Since no study to date has determined the feasibility of using the combined intervention of *Dexamethasone* and physical activity in fatigued patients with advanced cancer, the primary objective in this study is to obtain preliminary data for feasibility, adherence, and satisfaction with use of *PA+ Dexamethasone*. Variables to be evaluated include rates of participant recruitment and retention, frequency of use of the physical activity prescription and % of completion, the proportion of pills taken, acceptability of the physical activity and study drug to patients, and barriers to participation. Adherence will be calculated as the mean (across all patients) percentage of total prescribed endurance physical activity/walking minutes. Our experienced team is confident that we can successfully accrue the necessary number of study patients, based on the prior successful accrual of more than 500 patients in other fatigue treatment trials including studies involving combined therapies (NCT01410942) for CRF[39] that had eligibility criteria similar to those in our proposed study.[12,18-21,40]

Objective #2: To explore the preliminary efficacy of EX+ Hi Dex group and EX+ Lo Dex groups on CRF as measured by FACIT-F at the end of one week: To test this hypothesis, we will use a randomized controlled design. The primary outcome would be a change in FACIT-F subscale scores from baseline to Day 8.

FACIT-F is a well-validated QOL instrument.[43] This FACIT-F fatigue subscale was chosen as the primary outcome measure since it has been widely used in CRF treatment trials by our team and by others.[12,18,19,21,45] The 13-item fatigue subscale is a patient-rated assessment of intensity of fatigue and its related symptoms on a scale of 0 to 4. This scale has been shown to have strong internal consistency (α = 0.93–0.95), sensitivity of 0.92, and specificity of 0.6923.

Drug Intervention: Eligible patients randomized to receive a high-dose regimen [8 mg of dexamethasone orally, twice a day for 7 days] or low-dose regimen [4 mg of dexamethasone, twice a day for 7 days]. All patients will be given a proton pump inhibitor during the course of their treatment. During the study blood glucose will be monitored and hyperglycemia will be managed at the Supportive Care Center by the PI (Dr Sriram Yennu MD, MS) under the supervision of our Endocrine collaborator (Dr Busaidy) who will be consulted as necessary. We will collect blood samples at baseline and day 29 and patients will perform fasting finger sticks (after instruction) using the glucometer on day 3 (+/-1), day 8 (+/-1), and day 15 (+/-1) to monitor the blood glucose levels.

Physical Activity or Exercise Intervention: For this study, we plan to use a standardized physical activity intervention supervised by the Research Staff. We will use a combination of a supervised and home physical activity regimen. The weekly regimen will include a graded resistance physical activity program and a walking regimen. The graded resistance physical activity program has been designed to strengthen the major muscles of the lower body, including the quadriceps, hamstrings, gluteus maximus, and hip flexor group. These exercises will include (but will not be limited to) squats, lunges, leg extensions, leg curls, and hip extensions. The goal of the resistance exercises is to enhance the individual's ability to go from a seated to standing position independently. We plan to use resistance tubes as our mode of resistance. These tubes are color-coded to indicate their specific resistance level: light, moderate, or hard. The resistance exercise sessions are to be completed 3 days a week, allowing at least 48 hours between each session. This allows the muscles adequate time for rest and prevents overtraining. The graded resistance program will be designed so that the individual begins with a lighter resistance and progresses to heavier resistance once a level has been mastered. The participant will begin with 2 sets of 12 repetitions at the established intensity level. If the participant is not able to complete 2 sets of 12 repetitions for any one of the exercises assigned, we will ask them to do what they are able to with or without bands and document in the records. The individual will engage in a walking program. Since the level of aerobic fitness will vary among participants, the intensity and duration of the walking program will be established based on the initial evaluation by the exercise physiologist's assessment of the participant's current aerobic fitness level (six-minute walk test). The walking recommendation may vary in frequency and duration, but the intensity will be moderate. This intervention may include a 10-min walk 1-3 times a day at a moderate intensity level or up to a 30-min walk once a day at a relatively hard intensity level. To encourage and monitor adherence to the walking program, we will provide participants with a pedometer and an exercise log to record the number of steps they take each day. The participants will be asked to walk a minimum of 5 days a week at the duration established by the Research

Staff. At the first study visit, the research staff will meet with each participant to evaluate his or her current strength and aerobic fitness level and to teach the assigned exercises. Participants will be given an exercise log to record their resistance exercise sessions as well as their walking sessions. Participants will also receive a pedometer to be used during the entire intervention, which provides a tool to help them monitor their physical activity. They can set goals for the number of steps per day and record the steps on the pedometer to monitor their progress. They will receive weekly phone calls from the research staff after the initial in-person instructional meeting to assess their progress and to help them identify and overcome any barriers to completing the exercise program as a part of a formal behavioral support program (i.e., self-monitoring, goal setting, problem-solving overcoming barriers, cognitive restructuring, and rewarding oneself). The frequency, intensity, and duration of the assigned exercises will also be evaluated and adjusted as necessary.

D3. Measures: We will use the 30 second chair stand test, six-minute walk test, and an accelerometer. A self-report physical activity questionnaire, the Godin leisure-time physical activity questionnaire, will be used to complement the objective measures. A Myopathy questionnaire will be administered to assess patient-reported weakness due to myopathy (Appendix O) at baseline, Days 8, 15, 29, and one month after the last visit. Respironics Actiwatch 2 accelerometers will be used to objectively measure physical activity for patients who agree to this optional procedure. These accelerometers complement the self-report for estimating physical activity and can record physical activity in 2 minute increments for 30 days. Patients will wear the accelerometer for the four weeks they are on study. Physical activity data will be downloaded to a personal computer and converted to a measure of energy expenditure, after adjusting for patients' weight. The Satisfaction Scale (Appendix J) and Satisfaction Questionnaire (Appendix P) will be used to assess patient satisfaction. These questionnaires will be administered and physical performance measures performed on the last day the research nurse/ coordinator sees the patient. One month after the last visit, the questionnaires will be administered (in person or by telephone) and physical performance measures will be performed if the patient is in clinic.

Objective #3: To explore the effects of *PA+ Dexamethasone* on the various dimensions of fatigue (PROMIS), i.e., affective/emotional (HADS); physical/behavioral (MFSI-SF, ESAS, PSQI), physical activity and function (30 second sit-to-stand test, six minute walk).

A. PROMIS measures key symptoms and health concepts applicable to advanced cancer, enabling efficient and interpretable clinical trial research and clinical practice application of patient-reported outcomes (PROs).[45,46] The PROMIS fatigue measure used in the study was found to be highly correlated with the legacy measures.[9]

B. MFSI-SF consists of 30 items designed to assess the multidimensional nature of fatigue.[47] Ratings are summed to obtain scores for 5 subscales (general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor).

C. HADS: This 14-item questionnaire has been validated in a number of clinical situations and has been widely used in medically ill patients.[48]

D. **PSQI:** This instrument provides a brief, clinically useful assessment of a variety of sleep disturbances that might affect sleep quality. [49]

E. 30 second sit-to-stand test: The 30 second sit-to-stand test will be administered at baseline, Day 29, and one month follow up visit if the patient is in clinic. The 30 second sit-to-stand test will assess lower body strength.51 A standard chair without arms with an approximate height of 17 inches will be used. After a demonstration, a practice trial of one repetition will be done to check for proper form. On the start signal, the participant rises to a full stand and then returns to a fully seated position. The patient completes as many full stands as possible within a 30 second period. We will also assess the sit-to-stand test to monitor for myopathy. Previous studies also have suggested that physical activity would reduce the risk of myopathy due to steroids.

F. Six minute walk Test: The 6 minute walk test will be administered at baseline, Day 29, and one month follow up visit if the patient is in clinic. This will be used to assess physical function and has been recommended by the American Thoracic Society (ATS) as an objective measure of functional capacity. This test has been found to be an objective measure of functional capacity in patients with chronic respiratory conditions, fibromyalgia, stroke, and cancer. Our group has used this methodology in the assessment of fatigue and dyspnea. In the six-minute walk test, participants are asked to walk as fast and as far as they can for six minutes, and the distance walked is measured. The test will be conducted in an area with a 250 foot hallway and minimal traffic. The six-minute walk test has high test-retest and inter-tester reliability, and its validity is supported by correlations with self-report measures of fatigue and functional status [71]. The patient will be strongly encouraged to give a maximum effort.

G. Cytokine assessments/chemistries: Optional blood will be collected and stored for future cytokine research.

Chemistries to be collected include chloride, sodium, potassium, carbon dioxide, calcium, and glucose will be analyzed in the diagnostic center as standard of care.

During the study blood glucose will be monitored (Table 4). We will have our Endocrine collaborator (Dr Busaidy) who will work with us for patients that become hyperglycemic and will be consulted as necessary. We will collect blood samples at baseline and day 29 and patients will perform fasting finger sticks (after instruction) using the glucometer on day 3 (+/-1), day 8 (+/-1), and day 15 (+/-1) to monitor blood glucose levels.

Table 4. Study Assessments

ASSESSMENTS	BASELINE	DAY 8 (± 3)	DAY 15 (± 3)	DAY 21 (± 3)	DAY 29 (± 3)	1 month post study‡
History/Physical Exam	X				X	
Zubrod score	X					
Medication review	X	X	X	X	X	X
FACIT-F, ESAS , MFSI-SF, HADS, PSQI	X		X		X	X
PROMIS	X	X	X		X	X
Myopathy Questionnaire	X	X	X		X	X
Physical Performance tests (30 second chair stand test and 6 minute walk test)	X				X	X
Physical activity (pedometer, accelerometer, Godin leisure-time physical activity questionnaire)	X	X			X	X
Hematology/chemistry/optional blood	X	X©	X©		X	
Toxicity evaluation		X	X	X	X	X
Satisfaction Scale and Satisfaction Questionnaire					X	X

‡ The purpose of 1 month post-study is to assess the long-term effects of study treatment

© During the study, blood glucose will be monitored. We will have our Endocrine collaborator (Dr. Busaidy) who will work with us for patients that become hypoglycemic and will be consulted as necessary. We will collect blood samples at baseline and day 29 and patients will perform fasting finger sticks (after instruction) using the glucometer on day 3 (+/- 1), day 8 (+/-1) and day 15 (+/-1).

E. STATISTICAL CONSIDERATIONS:

The primary study objective is to assess the feasibility, adherence, and satisfaction with *Dexamethasone* combined with physical activity. If the patient states that they did participate in the study by taking at least a dose of drug or participated in any exercise intervention they are evaluable. To be considered adherent the patient needs to meet the adherence parameters of study drug, walking exercise and resistance exercise. For this study we will use only the available data provided by the patient to calculate feasibility. If no data is provided by the patient, then they will be considered non-compliant (if evaluable). If only one type of data (study drug or walking exercise or resistance exercise) is available, we will use the available data to consider adherence. If a patient provides two types of data then that patient would have to satisfy the adherence thresholds for both types of data to be considered "adherent". Adherence to study drug is defined as having taken at least 10 pills. Adherence to walking exercise is defined as at least 90 min every week. Adherence to resistance exercise is defined as at least 1.8 sets of exercises every week. The study will be considered feasible if > 75% of patients demonstrate adherence. Satisfaction is defined as any patient who choose options somewhat satisfied or completely satisfied. We will use either phone or exercise dairies to document compliance. With 35 patients in each arm, a 95% confidence interval for 0.75 would have a half width of 0.15. The key secondary end point of the study is the difference between the FACIT-F subscale score at baseline and at 8 days. We will estimate the mean difference in FACIT-F scores with 95% confidence intervals.

Sample Size Justification: Our prior data[16] [Fig.2], showed that 4mg twice a day of dexamethasone resulted in clinical relevant improvement (≥10 points change in the FACIT-F score) in 33% of patients. In this feasibility study, a change in FACIT-F subscale scores will be evaluated in the HiDex group (8mg orally of dexamethasone twice a day for 7days) and LoDex group (4mg orally twice a day of dexamethasone for 7days), both groups also will also undergo 4 weeks of physical activity intervention [See Treatment Schema Fig 5 below]. In order to obtain a reliable estimate of clinically relevant or robust improvement at Day 8, physical activity plus HiDex group in Physical Activity plus LoDex group, we need 35 in each group with a total sample size of 70. If the robust response proportions are 0.33 or 0.60, the half-widths of 95% confidence intervals will be 0.16. As this study is designed to be a non-comparative trial to assess feasibility, adherence and satisfaction, a sample size of 70 patients would be sufficient to evaluate the primary objective of this preliminary study and therefore no additional patients to account for dropouts are added.

To address issues related to missing data, we will perform multiple imputation analyses.[72] We recognize the potential need for steroids while receiving other therapies and we will collect the information and include as covariates in the secondary analysis. Since FACIT-F scores will be obtained at 0, 8, 15, 29, and 60 days, we will also analyze the data by using linear mixed effects longitudinal models. We will perform exploratory data analyses to assess treatment effects for other continuous outcome variables including MFSI-SF, PROMIS, HADS, and cytokine levels by using the same statistical methods described above. Before performing inferential procedures, we will conduct extensive descriptive statistical analyses of the outcome and predictor variables. Standard descriptive statistics, including means, standard deviations, ranges, and frequencies, will be computed where appropriate. Distributional characteristics of relevant variables will also be closely examined with use of box plots and histograms. If the data do not appear to be approximately normally distributed, transformations will be made to the data, or appropriate nonparametric methods will be used.

F. PROTECTION OF HUMAN SUBJECTS

We will obtain authorization for use and disclosure of Protected Health Information (PHI) from patients. This will be included in the written informed consent. We will follow The Health Insurance Portability and Accountability Act (HIPAA) guidelines during the study based on the following 3 criteria: 1) All research staff have completed research training concerning confidentiality of protected health information. Patient's name, social security number and other patient identifiers will not be used for data collection. Only protocol accession numbers will be used in data collection. The principal investigator will keep the collected data in a locked file cabinet; 2) Data collected for this study will be retained for 2 years after publication of the research and then it will be destroyed by a mechanic shredder; 3) The data will be used for this study only. Only the PI, the project

manager, the research nurse and the data manager will have access to the data. The data will not be disclosed to any other parties.

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