CANCER RELATED FATIGUE, EFFECT OF CANCER TREATMENT ON FATIGUE & EFFECT OF FATIGUE ON QUALITY OF LIFE

DISSERTATION SUBMITTED TO THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY, CHENNAI, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF MEDICINE BRANCH IX (RADIOTHERAPY) EXAMINATION - MARCH 2010

INSTITUTION
DEPARTMENT OF RADIATION ONCOLOGY
MADRAS MEDICAL COLLEGE, CHENNAI

The Tamilnadu Dr.M.G.R Medical University
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DECLARATION BY THE SCHOLAR

I hereby declare that the dissertation entitled "CANCER RELATED FATIGUE, EFFECT OF CANCER TREATMENT ON FATIGUE & EFFECT OF FATIGUE ON QUALITY OF LIFE" submitted for the Degree of Doctor of Medicine in BRANCH IX (RADIOTHERAPY), is my original work and the dissertation has not formed the basis for the award for any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or Institution for the award of any degree or diploma.

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CERTIFICATE

Certified that the dissertation "**CANCER RELATED FATIGUE, EFFECT OF CANCER TREATMENT ON FATIGUE & EFFECT OF FATIGUE ON QUALITY OF LIFE**" is a record of research work done by **Dr.NANDAN M SHANBHAG** during the period of his study under my guidance, and that the dissertation has not previously formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles and that is an independent work done by him.

Signature of the Guide

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INTRODUCTION

BACKGROUND
Global

Cancers in all forms are causing about 12 per cent of deaths throughout the world. In the developed countries cancer is the second leading cause of death accounting for 21% (2.5 million) of all mortality. In the developing countries cancer ranks third as a cause of death and accounts for 9.5% (3.8 million) of all deaths. Tobacco alcohol, infections and hormones contribute towards occurrence of common cancers all over the world.

India

Cancer has become one of the ten leading causes of death in India. It is estimated that there are nearly 1.5-2 million cancer cases at any given point of time. Over 7 lakh new cases of cancer and 3 lakh deaths occur annually due to cancer. Nearly 15 lakh patients require facilities for diagnosis, treatment and follow up at a given time. Data from population-based registries under National Cancer Registry Programme indicate that the leading sites of cancer are oral cavity, lungs, oesophagus and stomach amongst men and cervix, breast and oral cavity amongst women. Cancers namely those of oral and lungs in males, and cervix and breast in females account for over 50% of all cancer deaths in India.

WHO has estimated that 91 per cent of oral cancers in South-East Asia are directly attributable to the use of tobacco and this is the leading cause of oral cavity and lung cancer in India.

Cancer usually occurs in the later years of life and with increase in life expectancy to more than 60 years, an estimate shows that the total cancer burden in India for all sites will increase from 7 lakh new cases per year to 14 lakh by 2026.

During the last decade, there has been a growing recognition of the high prevalence of fatigue among cancer patients, its adverse effect on their quality of life, and the need to develop effective interventions to prevent or relieve it. This increased attention can be attributed, in part, to the development of instruments for the assessment of fatigue and their validation with cancer patients. These instruments have provided researchers with the tools necessary for quantifying and characterizing fatigue and exploring its aetiology and treatment.

LACUNAE

As per the NCCN Survey conducted in July 2006 the following graphs actually denote the minimal awareness & serious lacunae in the Oncology speciality to deal with Cancer Related Fatigue & its effect on quality of life of patients.

This study aims to address all these issues to bring about awareness and thus enabling better prophylactic and symptomatic interventions to correct the same.

REVIEW OF THE LITERATURE

CANCER RELATED FATIGUE is a very important symptom that most of the cancer patients have either before, during or after the treatment. It will be discussed below under following headings:

- Definition
- Significance
- Fatigue associated with cancer and its treatment
- Age & Cancer Related Fatigue
- Type of Cancer & Fatigue
- Causes
- The Relationship Between Cancer-Related Fatigue and Patient Satisfaction with Quality of Life in Cancer

DEFINING FATIGUE

A definition proposed by Cella and colleagues captures several of the more commonly described features of fatigue [2].

They define fatigue as, “a subjective state of overwhelming and sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest.”

With regard to assess-ment, three features of this definition are worth noting.

First, it identifies fatigue as a subjective phenomenon, implying that it can best be measured via self-report methods.

Second, it offers several ways in which fatigue may be distinguished from “nor-mal” tiredness. These include its severity and chronicity (“over-whelming and sustained exhaustion”) and its imperviousness to actions that typically provide relief from tiredness (“not relieved by rest”).

Third, there is an implication as to the clinical significance of this phenomenon and its multidimensional qualities (“decreased capacity for physical and mental work”)

SUMMARY: The assessment of fatigue in cancer patients is beset by a number of methodological challenges. The lack of a commonly agreed on definition of fatigue is perhaps the greatest challenge.

SIGNIFICANCE

In a cross-sectional, questionnaire-based survey to investigate cancer patients' experience of fatigue and their perceptions about the causes, management and impact of this symptom at three regional cancer centres; Glasgow, Birmingham and Southampton[3] of one thousand three hundred seven outpatients with cancer attending the three units over a 30-day period, the response rate was 576 of 1307 (44%). Fatigue was reported to affect 58% of patients 'somewhat or very much'. The comparable figures for pain and nausea/vomiting were 22% and 18%, respectively. Fatigue had never been reported to the hospital doctor by 52% (281 of 538) of patients with this symptom. Only 75 patients (14%) had received treatment or advice about the management of their fatigue. Fatigue was reported to be not well-managed by 33% (180 of 538) of patients with this symptom. The comparable figures for pain and nausea/vomiting were 9% (46 of 538) and 7% (37 of 538), respectively. The median FACT-F score was 18 (range 0-52). On multivariate analysis 54% of the variation in FACT-F scores could be explained by the combination of quality of life, depression, dyspnoea, weight loss/anorexia and use of analgesics in the previous month.

CONCLUSIONS: Fatigue has been identified as an important problem by patients with cancer. It affects more patients for more of the time than any other symptom and is regarded by patients as being more important than either pain or nausea/vomiting. Research into the aetiology and management of this symptom should be regarded as a priority.

AGE & CANCER RELATED FATIGUE

Although fatigue has been a focus for research in adult cancer care for some time, the same cannot be said for adolescent oncology practice. Drawing on data from four empirical studies[4], fatigue is multidimensional, multifactorial and highly subjective, but can be managed to enhance self-caring and coping strategies. All of the studies reviewed within indicate that fatigue is a troublesome symptom, which impacts on quality of life. From this review, we set up a research study. Concurring with the studies reviewed, findings from the preliminary data suggest that fatigue is a highly subjective and 'abnormal' phenomenon that holds a variety of implied meanings and associated metaphors connected with past experiences of childhood cancer. The focus group proved to be a viable research method to facilitate mutual disclosure and provoke discussion. Recognition of the research challenges with adolescents, where there is the potential for a range of meanings for the experience of fatigue, is an important finding for future studies.

In a study[5] of seventy-seven consecutive cancer patients with different tumors age 60+ served by the senior adult oncology program of the H. Lee Moffitt Cancer Center, were enrolled in the study. Inclusion criteria were: (1) age >-60 years; (2) histological diagnosis of malignancy; (3) no major psychiatric or neurological disorder that could interfere with the competition of the measures; (4) ability to understand and to speak English. Assessment included cognition, function, depression and fatigue. The instruments included geriatric depression scale, mini mental state examination and fatigue symptom inventory. The study used a cross-sectional design.

Fifty-six patients (72.7%) reported fatigue at the time of the assessment; seventy-six patients (99%) in the past week. Forty patients (52%) rated their average fatigue as greater than 5. Forty-two patients (54%) reported that they felt fatigue all seven days, for any part of the day in the week before the assessment. Sixty five (84%) patients rated fatigue as interfering with their general level of activity. The fatigue disruptiveness was higher for women than for man ($P<0.007$). Marital status and educational level were not significantly related to fatigue severity or fatigue disruptiveness ($P>$ or $=0.33$). A significant positive correlation between depressive symptoms and fatigue severity ($r = 0.29$, $P<0.01$) was recorded. Depression was also significantly related to fatigue disruptiveness ($r = 0.44$, $P<0.01$). Cognitive status was not correlated with fatigue severity or fatigue disruptiveness. A negative correlation between haemoglobin level and fatigue severity ($r = -0.30$, $P<0.01$) and between

haemoglobin level and fatigue disruptiveness (r = -0.28, P<0.01) was found. Having had medical care or counselling in the past for anxiety and depression was positively correlated with fatigue disruptiveness (r = 0.29, P<0.01).

CONCLUSION: Fatigue is a common symptom of older & adolescent cancer patients on treatment.

TYPE OF CANCER & FATIGUE

BREAST CANCER[6]

In a literature review[6] to evaluate the prevalence and course of fatigue in patients with breast cancer undergoing adjuvant chemotherapy and to examine factors relating to fatigue, fatigue was one of the most common side effects of cancer treatment.

High and fluctuating prevalence rates of fatigue have been found not only during but also after adjuvant chemotherapy. The intensity of fatigue seems to be stable throughout the treatment cycles, despite the common perception that more chemotherapy treatments lead to greater fatigue.

OVARIAN CANCER[7]

Although fatigue is a commonly reported symptom in cancer patients it is rarely investigated, especially in patients with ovarian carcinoma.

Ninety-eight ovarian carcinoma survivors (average age of 57.4 +/- 12.5 years) were included in the study. All women had received cancer therapy but had not been treated for at least 6 months. The average time elapsed since first diagnosis was 5.7 +/- 5.5

years. Fatigue was measured with the Multidimensional Fatigue Inventory (MFI-20) and QOL was measured with the Functional Assessment of Cancer Therapy (FACT)-ovarian carcinoma part and the European Organization for Research and Treatment of Cancer Care Questionnaire, including the ovarian carcinoma module.

Thirty-two of 98 ovarian carcinoma patients (32.7%, 95% confidence interval, 23.5-42.9%) reported MFI-20 General Fatigue scores >/= 12.0 and therefore could be characterized as suffering from fatigue. This group of patients had a significantly lower QOL, had higher scores of anxiety and depression, and perceived that they had less social support. In a multiple regression model, mental adjustment, social support, anxiety, and depression as well as fatigue were significant predictors of QOL (FACT-generic part total score) whereas clinical and sociodemographic variables were not.

A remarkably high proportion of ovarian carcinoma survivors suffered from fatigue. Because this symptom is a key predictor of QOL, it should be given more attention in aftercare programs.

Among 287 epithelial ovarian cancer survivors treated according to protocols at The Norwegian Radium Hospital between 1977 and 2003, 189 patients (66%) participated. Information was collected by a questionnaire containing demographic and morbidity items and self-rating scales. Internal comparisons of various subgroups of epithelial ovarian cancer survivors were performed, and epithelial ovarian cancer survivors were compared with age-adjusted controls from the general population.

Minimal differences were observed relating to somatic and mental morbidity, fatigue, and QOL between epithelial ovarian cancer survivors with and without relapse, long or short follow-up time, and prognostic index status. Chronic fatigue was found in 22% (95% CI, 16% to 28%), and only body image was significantly associated with chronic fatigue in multivariable analyses. Epithelial ovarian cancer survivors showed significantly more somatic and mental morbidity, somatic complaints, use of medications, and use of health care services than controls. The levels of anxiety and fatigue were also significantly higher in epithelial ovarian cancer survivors than in controls, whereas the levels of depression and of several QOL dimensions were lower. The prevalence of chronic fatigue was 12% among controls.

Epithelial ovarian cancer survivors had more somatic and mental morbidity, more fatigue, poorer QOL, and used more medication and health services than controls. Minimal differences were observed between various epithelial ovarian cancer survivors subgroups. Health care professionals should try to improve and be attentive to the health of epithelial ovarian cancer survivors.

HAEMATOLOGICAL MALIGNANCIES [8]

In a study to describe fatigue severity, fatigue interference, and associated factors in hematologic malignancies.

Patients being treated for leukemia and non-Hodgkin's lymphoma (n = 228) completed the Brief Fatigue Inventory to rate fatigue severity and functional interference caused by fatigue. Data on patient demographics, Eastern Cooperative

Oncology Group performance status, other physical symptoms, current treatments, and laboratory values were also collected. Descriptive statistics, bivariate correlation, and logistic regression were used for data analysis.

Fifty percent of the sample reported severe fatigue, which was defined as a "fatigue worst" rating of 7 or greater. More patients with acute leukemia (61%) reported severe fatigue compared with those with chronic leukemia (47%) and non-Hodgkin's lymphoma (46%). Increased fatigue severity significantly compromised patients' general activity, work, enjoyment of life, mood, walking, and relationships with others. Fatigue severity was strongly associated with performance status, use of opioids, blood transfusions, gastrointestinal symptoms, and sleep disturbance items, as well as with low serum hemoglobin and albumin levels. Regression analysis indicated that nausea was the significant clinical predictor of severe fatigue (odds ratio, 13), and low serum albumin was the significant laboratory value predictor (odds ratio, 3.8). Disabling fatigue occurs with high frequency in hematologic malignancy, supporting a need to develop better methods of fatigue management. Better control of gastrointestinal and other symptoms may be of benefit. The mechanism and relationship between low albumin and severe fatigue needs to be investigated further, and longitudinal studies of the effects of treatment, host factors, and other symptoms are needed.

LUNG CANCER [9]

The medical records of 50 consecutive patients receiving radiation therapy for histologically diagnosed lung cancer were retrospectively reviewed to determine the frequency of fatigue and its relationship to pain, depression, and other potentially treatable correlates.

Fatigue developed in 39 of the 50 patients (78%), and was not strongly related to demographic or disease variables. Pain was experienced by 40 patients (80%), but depression was noted in the records of only six patients (12%). Onset of fatigue closely followed development of pain in only 11 patients. Lower frequency of fatigue in patients with previous surgery or chemotherapy and the likelihood of a response shift suggest these were not significant causes of fatigue. Previous studies highlight a higher frequency of depression in cancer patients and a correlation with treatment-related fatigue. Prospective studies on the relationship between depression and fatigue and the ability of antidepressants to ameliorate treatment-related fatigue are needed.

In 573 advanced non-small-cell lung cancer patients enrolled in a phase III clinical trial [10], who used baseline and 6-week follow-up PRH scores to predict best response to treatment, disease progression, and survival. Using regression analyses, when tested the predictive ability of the five subscales of the Functional Assessment of Cancer

Therapy-Lung (physical, functional, social/family, emotional well-being, and the lung cancer subscale) as well as the trial outcome index (TOI) aggregate score.

After clinical factors were controlled for, baseline physical well-being (PWB) and TOI scores predicted all three clinical outcomes. A higher baseline PWB score was associated with a better response to treatment (odds ratio, 1.09; P <.001) and lower risk of death (risk ratio, 0.95; P <.001). Higher baseline TOI score was associated with a lower risk of disease progression (risk ratio, 0.98; P <.001). These two baseline predictors (PWB and TOI) were then used along with 6-week change scores to classify patients into four groups: low baseline-declined, low baseline-improved, high baseline-declined and high baseline-improved. Patients with low baseline-declined PWB scores showed the worst responses to treatment and survived the shortest duration. Patients with low baseline-declined TOI scores had the shortest time to progression.

The physical aspects of baseline PRH and PRH change during chemotherapy are significant predictors of clinical outcomes in lung cancer. This has implications for patient stratification in clinical trials and may aid decision-making in clinical practice.

INCURABLE CANCER ? [11]

The suffering of patients with incurable cancer is determined to a large degree by the presence and intensity of the symptoms of their disease. Knowledge of symptom prevalence is important for clinical practice. The main aim of this study was to obtain

a reliable estimation of symptom prevalence in patients with incurable cancer by performing a systematic review of studies assessing this topic.

44 studies (including 25,074 patients) on overall symptom prevalence (Group 1) and six studies (including 2,219 patients) on symptom prevalence during the last one to two weeks of life (Group 2). In these studies, symptom prevalence was assessed by a questionnaire, a standardized interview, or the medical record. 37 symptoms assessed in at least five studies were identified.

Almost all symptoms occurred in more than 10% of the patients. Five symptoms (fatigue, pain, lack of energy, weakness, and appetite loss) occurred in more than 50% of the patients of Group 1. Weight loss occurred significantly more often in Group 2 compared to Group 1, and pain, nausea, and urinary symptoms occurred significantly less often. Generally, symptom prevalence was highest if assessed by a questionnaire. The results of this study should be used to guide doctors and nurses in symptom management. Proper attention to symptom burden and suffering should be the basis for individually tailored treatment aimed at improving or maintaining quality of life of patients in their last period of life.

Conclusion: Fatigue is present in all cancer patients to varying degree irrespective of the site and histopathology

Fatigue associated with cancer and its treatment

In a study [12] designed to confirm the prevalence and duration of fatigue in the cancer population and to assess its physical, mental, social, and economic impacts on the lives of patients and caregivers. A 25-minute telephone interview was completed with 379 cancer patients having a prior history of chemotherapy. Patients were recruited from a sample of 6, 125 households in the United States identified as having a member with cancer. The median patient age was 62 years, and 79% of respondents were women. Patients reporting fatigue at least a few times a month were asked a series of questions to better describe their fatigue and its impact on quality of life.

Seventy-six percent of patients experienced fatigue at least a few days each month during their most recent chemotherapy; 30% experienced fatigue on a daily basis. Ninety-one percent of those who experienced fatigue reported that it prevented a "normal" life, and 88% indicated that fatigue caused an alteration in their daily routine. Fatigue made it more difficult to participate in social activities and perform typical cognitive tasks. Of the 177 patients who were employed, 75% changed their employment status as a result of fatigue. Furthermore, 65% of patients indicated that their fatigue resulted in their caregivers taking at least one day (mean, 4.5 days) off

work in a typical month. Physicians were the health care professionals most commonly consulted (79%) to discuss fatigue. Bed rest/ relaxation was the most common treatment recommendation (37%); 40% of patients were not offered any recommendations.

Cancer-related fatigue is common among cancer patients who have received chemotherapy and results in substantial adverse physical, psychosocial, and economic consequences for both patients and caregivers. Given the impact of fatigue, treatment options should be routinely considered in the care of patients with cancer.

Fatigue is often related to cancer, and that related to its treatment is the most commonly reported side effect of cancer treatment. It differs from that induced by other causes, such as sleep disturbance and exertion, as the latter are typically alleviated by a period of rest. In contrast to exercise-induced fatigue, the fatigue reported by cancer patients is usually described as an unusual, excessive, whole-body experience that is disproportionate or unrelated to activity or exertion and is not relieved by rest or sleep. Cancer-related fatigue is a subjective experience that has a clear detrimental effect on a cancer patient's quality of life and ability to sustain the usual personal, professional, and social relationships. The fatigue can be pervasive:

cancer patients frequently report that fatigue begins with treatment, continues during the course of chemotherapy or radiation treatment, and declines somewhat - but frequently sustains at a higher-than-baseline rate - after treatment is over. It may also persist for several years even in patients with no apparent disease. While a number of researchers have speculated about the nature of cancer-related fatigue, there has been little systematic research on its etiology or treatment. In many aspects our knowledge of the fatigue mechanisms in cancer patients is at a similar stage to that reached in our understanding of anti-cancer therapy-induced nausea and vomiting about 20 years ago. This paper introduces four plausible hypotheses for the development of fatigue. Evidence available to support a role for anemia, adenosine triphosphate, vagal afferents, and the interaction of the HPA/cytokines and 5HT is discussed.[13]

A study[14] was conducted to assess symptom prevalence and symptom intensity and their relation to quality of life in medical oncology patients at a Veterans Affairs medical center.

Consecutive inpatients and outpatients were asked to complete the Functional Assessment Cancer Therapy (FACT-G), Memorial Symptom Assessment Scale (MSAS), and the Brief Pain Inventory. Symptoms then were analyzed by their relation to Karnofsky performance status (KPS) and quality of life.

Two hundred forty patients participated. The median number of symptoms was 8 per patient (range, 0-30 symptoms). The 5 most prevalent symptoms were lack of energy (62%), pain (59%), dry mouth (54%), shortness of breath (50%), and difficulty sleeping (45%). Patients with moderate intensity pain had a median number of 11 symptoms and patients with moderate intensity lack of energy had a median number of 13 symptoms. The number of intense symptoms increased as the KPS decreased ($P < 0.001$). Patients with moderately intense pain or fatigue also were more likely to experience nausea, dyspnea, and lack of appetite. The number of symptoms rated as present on the Memorial Symptom Assessment Scale was found to correlate significantly with the FACT-G Sum Quality of Life score.

Intense symptoms were highly prevalent in this population. The presence of pain, lack of energy, or poor performance status should lead to comprehensive symptom assessment. Patients free of disease nevertheless still may experience intense symptoms. The number of symptoms present may be a helpful guide to quality of life. Routine comprehensive symptom assessment may identify a significant fraction of patients who urgently require intensive symptom palliation.

Cancer patients undergoing radiotherapy frequently report fatigue [15]. However, knowledge of the importance of fatigue for these patients and of the factors associated

with their fatigue is limited. The aim of the current investigation was to gain more insight into fatigue as related to radiotherapy by answering the following questions.

First, how is the experience of fatigue best described? Secondly, to what extent is fatigue related to sociodemographic, medical (including treatment), physical and psychological factors? Finally, is it possible to predict which patients will suffer from fatigue after completion of radiotherapy? Patients with different types of cancer receiving radiotherapy with curative intent (n = 250) were interviewed before and within 2 weeks of completion of radiotherapy.

During treatment, patients rated their fatigue at 2-weekly intervals. Results indicate a gradual increase in fatigue over the period of radiotherapy and a decrease after completion of treatment. Fatigue scores obtained after radiotherapy were only slightly, although significantly, higher than pretreatment scores.

After treatment, 46% of the patients reported fatigue among the three symptoms that caused them most distress. Significant associations were found between post-treatment fatigue and diagnosis, physical distress, functional disability, quality of sleep, psychological distress and depression. No association was found between fatigue and treatment or personality characteristics. Multivariate regression analysis

demonstrated that the intensity of pretreatment fatigue was the best predictor of fatigue after treatment. In view of this finding, a regression analysis was performed to gain more insight into the variables predicting pretreatment fatigue. The degree of functional disability and impaired quality of sleep were found to explain 38% of the variance in fatigue before starting radiotherapy. Fatigue in disease-free patients 9 months after treatment was observed.

Although studies show that cancer patients consider fatigue as an important problem, few, if any, studies have quantified the impact of fatigue on overall quality of life (QoL) in cancer patients. In recent study, evaluation of the relative impact of different QoL domains/subscales, including fatigue, on overall QoL in cancer patients preceding radiotherapy was done [16].

Sixty-four patients with lung or breast cancer selected for high-dose radiotherapy on the primary tumour completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Multivariate models were fitted to define the impact of QLQ-C30 subscales, including fatigue, on overall QoL.

Of all QLQ-C30 subscales, fatigue showed by far the strongest univariate correlation with overall QoL ($r = -0.76$, $P < 0.001$); correlations for functioning subscales ($r = 0.44$-0.55) and symptom subscales ($r = -0.31$ to -0.45) were considerably lower. In multivariate analyses, adjusting for potential confounders, fatigue was the only

subscale that independently contributed to overall QoL (standardized regression coefficient-0.57, $P < 0.001$).

Results indicated that, of all QoL domains/subscales, fatigue is by far the predominant contributor to patient-perceived overall QoL in both lung and breast cancer patients preceding high-dose radiotherapy.

Causes of Fatigue

The specific mechanisms involved in the development of cancer related fatigue are not completely known. Various factors play a part in the development of Fatigue. Several studies have reported different mechanisms and causes of Fatigue but only few of them are proven.

The causes of fatigue can be broadly divided into

Nutrition and metabolism

Medications

Co-morbid conditions

Psychosocial and Cognitive factors

Cancer therapies

Nutrition and metabolism

The nutritional requirements and metabolism are altered in cancer patients. There is decreased availability of metabolic substrates due to increased energy demand by the normal tissues for fighting against the growing tumor. Tumor

consumption of available nutrients, hypermetabolic condition due to tumor growth, associated infections and fever result in increased energy requirements. Moreover there is also reduced energy support due to cancer cachexia, nausea, vomiting, diarrhea and intestinal malabsorption. Due to all these factors there is impaired glucose, lipid and protein metabolism which ultimately results in abnormal production of substances (eg. cytokines or antibodies). These inhibit metabolism or normal muscle function, cause neurophysiologic changes of skeletal muscles, chronic stress response and hormonal changes. One very important factor which has been proven to directly affect fatigue is anemia. Anemia may be caused directly by the impaired nutrition or disease itself or Myelosuppression due to treatment itself.

Medications

Drugs other than chemotherapeutic agents like analgesics, antiemetics, antidepressants, anti histaminics, cough suppressants and antacids which have sedative effects (either as main or side effect) invariably contribute to fatigue.

Co morbid conditions

Other co-morbid conditions which may be present like infections, dehydration, lung diseases, liver failure, cardiac diseases, renal failure thyroid disorders also add to the fatigue

Psychosocial and Cognitive factors

Most of the cancer patients are very anxious about the outcome of the disease and treatment. There is also associated depression, stress, mental fogginess and decreased attention span. Because of all these there is sleep disturbances also which put together causes fatigue. The cancer patients withdraw themselves from the social interaction due to the diagnosis of cancer and its treatment.

Cancer therapies[13,14,15,16]

Several factors may place the surgical patient at risk of fatigue. These include the effects of anaesthesia, analgesia, and sedation, decreased ventilatary capacity, immobilization, infection, pre and post operative starvation, altered sleep patterns and anxiety. Fatigue after surgery may be compounded in cancer patients who receive adjuvant treatment, as they have often not recovered their energy levels before starting further treatment.

The way by which chemotherapy affects fatigue has not been fully understood. Many chemotherapy regimens (especially platinum based drugs) cause cumulative anemia, resulting in decreased oxygen supply. Also patients can also develop neutropenia and infection which may result in fatigue. Some drugs (bleomycin, adriamycin, BCNU, epirubicin, mitozantrone and mitomycin) may cause cardiac toxicities, neurotoxicities (methotrexate, ifosphamide,cisplatin, vincristine,

paclitaxol). It has also been noted that patients treated with biological therapies like interferon, interlukin, colony stimulating factors and tumor necrosis factor experience fatigue. In several studies fatigue is the most frequently reported dose limiting toxicity of biological therapy and has caused patients to refuse further treatment.

It is not known how radiotherapy causes fatigue. However it may be associated with increased energy needed to repair damaged epithelial tissue caused by radiation.

Summary: Fatigue is caused due to nutritional and metabolic impairment, associated co morbid condition, and medications, psychosocial factors and also due to treatment modalities.

FATIGUE & QUALITY OF LIFE

Fatigue affects a majority of patients undergoing cancer-related therapies.

A study of 954 adult cancer patients was conducted between April 2001 and November 2004 to quantify the relationship between fatigue and patient satisfaction with quality of life (QoL)[17].

Fatigue was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire fatigue subscale.

Patient satisfaction with QoL was measured using the Ferrans and Powers Quality of Life Index (QLI).

The relationship between fatigue and QLI was evaluated using univariate and multivariate linear regression after controlling for the effects of clinical and demographic factors. Of the 954 patients, 579 were females and 375 males, with a median age at presentation of 56 years (range 20-90 years). Sixty-six percent had failed prior treatment. The most common cancers were breast (26%), colorectal (19%), and lung (16%) cancers.

After controlling for the effects of age and prior treatment history, every 10-unit increase in fatigue was statistically significantly associated with 1.5-, 0.22-, 0.77-, 0.27-, and 0.85-unit declines in QLI health and physical, social and economic, psychological and spiritual, family, and global function scores, respectively. Consequently, a 30-point increase in fatigue score correlates with a 4.5-point decline in QLI health functioning-a clinically significant decline.

The impact of fatigue on the quality of life of oncology patients is substantial and under-recognized. Fatigue in these patients may begin with a simple decrease in physical activity, but can progress to include a wide range of negative effects that often culminate in patients feeling out of control, lonely, and isolated. In general, surviving cancer patients experience some limitations after the end of treatment but ultimately attain a reasonably good level of functioning.

An examination of subpopulations and further analyses of data suggest, however, four different recovery patterns [18].

Patients may:

A) improve in their functioning, reach a plateau at approximately year 2 or 3, and then remain at relatively high levels of functioning;

B) improve initially, but deteriorate again after year 2 or 3, never reaching the normal stage;

C) improve, returning to normal; or

D) have a very mixed pattern of high levels of fatigue that is, to date, very difficult to interpret.

Disturbingly, 60% of the survivors in our population of patients with Hodgkin's disease, who were treated in recent trials of the German Hodgkin Study Group and the European Organization for Research and Treatment of Cancer Lymphoma Group, had medium to high levels of fatigue after 5 cancer-free years. Investigations are essential to determine the current status of long-term survivors in more detail and to link that status to conditions observed during the treatment of acutely ill patients.

Data obtained from one academic hospital and two general hospitals in the Netherlands [19]. 235 patients who had a primary diagnosis of cancer and underwent treatment with curative intent were included. The rate of return to work was measured at 6, 12 and 18 months. Hazard ratios (HRs) for the duration of sick leave up to 18

months following the first day of sick leave were calculated. The rate of return to work increased from 24% at 6 months to 64% at 18 months following the first day of sick leave. Fatigue, diagnosis, treatment type, age, gender, depression, physical complaints and workload were all related to the time taken to return to work. Fatigue scores were also strongly related to diagnosis, physical complaints, and depression scores. Fatigue at 6 months predicted a longer sick leave with a hazard ratio of 0.71 (95% Confidence Interval (C.I.) 0.59-0.85), adjusted for diagnosis, treatment type, age and gender. In a multivariate Cox regression analysis, diagnosis, treatment, age, physical complaints and workload remained the only significant predictors of duration of the sick leave. 64% of cancer survivors returned to work within 18 months. Fatigue levels predicted the return to work. This was independent of the diagnosis and treatment, but not of other cancer-related symptoms. Better management of cancer-related symptoms is therefore needed to facilitate the return to work of cancer patients.

A study [20] was evaluated whether diagnostic criteria for cancer-related fatigue syndrome (CRFS) could be rigorously applied to cancer inpatients, and to explore the relationship between subjective fatigue and objective measures of physical activity, sleep, and circadian rhythm. Female cancer patients (n=25) and a comparison group of subjects without cancer (n=25) were studied. Study participants completed a structured interview for CRFS and questionnaires relating to fatigue, psychological symptoms, and quality of life (QoL). Wrist actigraphs worn for 72 hours were used as

an objective measure of activity, sleep, and circadian rhythm. Compared to controls, cancer patients were more fatigued, had worse sleep quality, more disrupted circadian rhythms, lower daytime activity levels, and worse QoL. After exclusion of subjects with "probable" mood disorders, the prevalence of CRFS was 56%. Fatigue severity among the cancer patients was significantly correlated with low QoL, depression, constipation, and decreased self-reported physical functioning. It can be concluded that the diagnostic criteria for CRFS can be applied to cancer inpatients but strict application requires a rigorous assessment of psychiatric comorbidity. Despite cancer inpatients having greater impairments of sleep and circadian rhythm, it was found that fatigue severity did not appear to be related to these impairments.

EVALUATION OF FATIGUE & QOL

UNIDIMENSIONAL AND MULTIDIMENSIONAL MEASURES OF FATIGUE

In the absence of a commonly agreed on definition of fatigue, it is not surprising that there is a lack of consensus about the optimal approach to assessing fatigue in cancer patients. Although the importance of obtaining patient self-reports is widely acknowledged, a variety of self-report instruments are currently in use. Much of the time, fatigue is assessed using a single item embedded in a symptom checklist such as the Symptom Distress Scale [21] or the Rotterdam Symptom Checklist [22].

Single-item visual analog scales and Likert-type scales are also often used to assess fatigue. Because of their single-item format, these measures have limited reliability and provide only the most perfunctory information about patients' experiences with

fatigue. Fatigue is also often assessed using multi-item measures such as the Fatigue Scale of the Profile of Mood States [23]. Although these multi-item measures generally possess better psychometric properties than single-item measures, most are limited in that they provide information only about a patient's general level of fatigue severity. In a more comprehensive approach, several investigators have developed and validated multidimensional measures of fatigue for use with cancer patients. Such measures include the Brief Fatigue Inventory [24], the Revised Piper Fatigue Scale [25], the Cancer Fatigue Scale [26], the Revised Schwartz CancerFatigue Scale [27], the Multidimensional Fatigue Inventory [28],and the Multidimensional Fatigue Symptom Inventory [29]. A recent publication provides information about the format of these and other measures and summarizes their psychometric properties [30]. Inspection of these measures indicates that there is little consensus at this time about the dimensional structure of fatigue in cancer patients (see Table 1). For example, one measure characterizes fatigue in terms of general, mental, and physical dimensions[31], whereas another measure characterizes it in terms of behavioral/severity, affective meaning, sensory, and cognitive/mood dimensions .The Fatigue Symptom Inventory (FSI), a measure developed by a research group for the multidimensional assessment of fatigue. The FSI is a 14-item measure that assesses the severity, frequency, and diurnal variation of fatigue, as well as its per-ceived interference with quality of life. Severity is measured using four separate items that assess most, least, and average fatigue in the past week as well as current fatigue.

Frequency is measured using two separate items that assess the number of days in the past week that respondents felt fatigued as well as the portion of each day on average they felt fatigued. Diurnal variation is measured using a single item that provides descriptive information about daily patterns of fatigue. Perceived interference is measured using seven separate items that assess the degree to which fatigue in the past week was judged to interfere with general level of activity, ability to bathe and dress, normal work activity, ability to concentrate, relations with others, enjoyment of life, and mood. The interference ratings can also be summed to yield a total interference score. Preliminary evidence of the reliability and validity of the FSI has been reported for women with breast cancer and for men and women with a variety of cancer diagnoses .

QUALITY OF LIFE

1. **FACT -** The Functional Assessment of Cancer Therapy - consists of the FACT-G
2. **European Organization for Research and Treatment of Cancer QOL Questionnaire** — The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - EORTC OLQ-C30 [. This scale includes items assessing symptoms and side effects , and appears to be sensitive to temporal

TABLE 1

changes before, during and after treatment with surgery, radiation therapy (RT), and chemotherapy

3. **University of Washington Quality of Life** — The University of Washington Quality of Life (UW-QOL) questionnaire is a self-administered scale consisting of 15 questions assessing nine domains including pain, physical appearance, activity, recreation, employment, chewing, swallowing, speech, shoulder function, and overall QOL. One study of 29 patients undergoing resection of oral cancer compared the EORTC QLQ H & N35 with the UW-QOL. The two scales were found to be complementary rather than duplicative. The authors concluded that although the UW-QOL provided less specific information compared to the EORTC QLQ H & N35, it was shorter and easier to use.
4. **Quality of Life Radiation Therapy Instrument** — A head and neck module has been developed for the quality of life - radiation therapy instrument (QOL-RTI)

AIMS AND OBJECTIVES

- To determine the magnitude of fatigue in Cancer Patients
- To determine the effect of Cancer Treatment (Chemotherapy, Radiotherapy) on fatigue.
- To determine the effect of Fatigue on Quality of Life.

MATERIALS AND METHODS

DISCLOSURES

This study was done purely in the Government hospital after obtaining the consent from the involved patients. The Tamil consent form is attached (appendix II)

Ethical Committee clearance was obtained prior to the study.(appendix I)

The license required to use the FACT-G in this study was obtained (appendix IV)

The validity & reliability report for the FACT-G also obtained (appendix V)

The study was periodically reviewed & presented in the department during the course.

Estimation of Sample Size

The estimation of sample size is based on the study "**Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer Fatigue Forum.AU - Stone P et al**". The sample size is estimated based on 5% significance level and with an error of 0.6. The sample size required is 110.

Sampling procedure

120 patients with histologically proven cancer, receiving Cancer Treatment in the Radiation Oncology department of Madras Medical College FEBRUARY 2009 to September 2009 were the subjects of the study.

Inclusion criteria

- Patients above 15 years.
- Patient with histological documentation of Cancer.
- Patients receiving External Beam Radiotherapy or Chemotherapy.
- Patients with Karnofsky Performance Status(KPS) 70 and above

Exclusion criteria

- Patients below 15 years.
- Patients with KPS<70

Data Collection

Common Toxicity Criteria –Fatigue, Functional Assessment of Cancer Treatment - G , TAMIL version for Fatigue and Quality of Life respectively were used in this study. Answers to the questionnaires on fatigue and quality of life will be filled by all the patients of the study by means of personal interview, before start of treatment, every week during the treatment and one month post treatment. For patients who did not know to read and write, were explained about the questionnaire in their mother tongue and response noted by the person interviewing.

TABLE 2

RESULTS

Statistical software:

The Statistical software namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

MALE: FEMALE:

FIGURE 1

Of the 120 patients 30(25%) were females & 90 (75%) males (FIGURE 1)

AGE:

FIGURE 2

AGE	FEMALES	MALES
15-20	1	4
21-30	5	4
31-40	8	11
41-50	8	25
51-60	3	25
>60	5	21

TABLE 3

61 (50%) patients were between the age of 40-60 years.26 (18%) were above 60 years (FIGURE 2 & TABLE 3)

SITE:

Figure 3

SITE	N = 120
Head & Neck	51
BREAST	11
CERVIX	8
CNS	21
LUNG	10
GastroIntestinal	8
Genito-Urinary	4
LYMPHOMA	2
ALL	2
Metastasis of Unknown Origin	2
Soft Tissue Sarcoma	1

Table 4

TREATMENT POLICY:

FIGURE 4

POLICY	N=120
PALLIATIVE	30
CURATIVE	90

TABLE 5

30(25%) patients underwent palliative treatment while 90(75%) Curative.
(Figure 4 & Table 5)

MODALITY:

Figure 5

While a single modality of treatment is offered to early stage diseases (Stage I & II) , most of the patients who reported to our department were locally advanced cases (Stage III & IV) for whom combined modality of treatment is the treatment of choice.

16(14%) patients were treated with Radiotherapy only. Treatment being mostly palliative. 63(51%) patients were treated with Chemo-Radiotherapy.
41(33%) were treated with all the three arms of Surgery, Chemotherapy & Radiotherapy

FATIGUE:

Figure 6

As it is evident on the figure 6 most of the patients reported with a mild level of fatigue to begin with.

Most importantly the majority of the conversion from mild to moderate & severe fatigue was during the 4^{th} & 5^{th} week of the treatment ($p = <0.005$)

Another important point to be noted is that 111(90%) never reached their pretreatment levels of fatigue, even at follow up

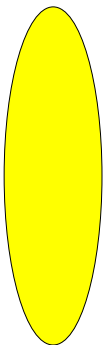

FIGURE 7

The mean average scores for the Physical well being of the patients suggest that the physical well being was adversely affected as treatment continued.

Figure 8

The social wellbeing denoting the relationship of the patient with his surroundings, friends & family was adversely affected too with the mean average scores declining on the weekly basis.The scores improved during the follow up though. (p=0.15)

Figure 9

The ability of the patient to cope with one's self was affected with the mean average scores declining as weeks of treatment progressed. The scores remained at the low levels even at follow up when the patient. This perhaps denotes very important criteria as the patient's will to live & cope with life after being affected by cancer is a crucial factor.

Figure 10

The ability of the patient to get back to his/her normal daily activities & work as he/she performed prior to the disease is denoted by the Functional Well Being.This though declined as other parameters but was by far the only parameter to reach its almost pre-treatment levels.(p=0.05)

Figure 11
Figure 12

Overall Quality of Life & its individual aspects were adversely affected as the treatment progressed as noted in the Figure 11 & Figure 12.The mean average scores did not reach the pre-treatment level scores even during the follow up.

Physical well being & Emotional Well Being were affected the most. Functional well being scores improved after treatment.

DISCUSSION

Despite the well-documented prevalence of fatigue in patients diagnosed with cancer, cancer-related fatigue (CRF) remains a widely under-reported and under-treated phenomenon. If advances in health care provision are to be successful in minimizing the suffering and distress caused by cancer-related fatigue an understanding of how people communicate its impact to family, friends, and healthcare professionals, and what meanings they ascribed to be, is essential. Although the word "fatigue" is understood by the scientific community it is unclear whether patients will spontaneously refer to their feeling of lack of energy, weakness, sleepiness, lack of motivation, desire for rest, etc. as "being fatigued."

The purpose of this research was to draw on qualitative research to explore how patients with cancer-related fatigue describe it.

The most salient finding was that in most of the studies cancer-related fatigue was reported as being of greater intensity than previously experienced tiredness, contributing to the general feeling that cancer-related fatigue was 'overwhelming' as well as abnormal. Furthermore, patients emphasized that cancer-related fatigue differed from their previous experiences of tiredness in its duration/persistence even after rest. Although triggers could be identified by some patients (e.g., chemotherapy), others conveyed the fact that cancer-related fatigue's unpredictability added to the frustration/despair and cognitive distress (e.g., inability to focus, inability to make decisions). Patients also reported a lack of motivation for engaging in activities with friends or family and a preference for staying by themselves to rest.

This study mainly aims to answer one most important question of all & in the end poses a question by itself.

IS CANCER RELATED FATIGUE REAL?

That is the question that this study answers with a resounding yes! & poses a challenge & a new question ,

IF IT IS A REAL SYMPTOM , THEN WHY NOTHING MUCH IS DONE ABOUT IT IN DAY TO DAY PRACTICE?

The answer lies probably in the literature about the various options available for the treatment of Cancer related Fatigue.

Review of Treatment Options

INTERVENTIONS — Management of cancer-related fatigue involves specific treatment for potentially reversible causes (ie, treating anemia or metabolic or endocrine abnormalities, as well as managing pain, insomnia, depression, or anxiety) and symptomatic measures when no obvious etiology or reversible cause can be identified. Nonspecific symptomatic treatment measures include education, counseling, and pharmacologic (eg, psychostimulants) as well as nonpharmacologic (eg, exercise, yoga, acupuncture) measures.

Management of anemia — Anemia is the most common reversible cause of cancer-related fatigue, particularly among patients receiving chemotherapy. Optimal management of symptomatic anemia requires an accurate diagnosis to identify potentially remediable causes (eg, ongoing blood loss, hemolysis, iron, folic acid, or vitamin B12 deficiency). If a potentially treatable cause cannot be identified, treatment options include red blood cell (RBC) transfusion, or for patients with chemotherapy-related myelosuppression, an erythropoietin stimulating agent (ESA).

ESAs — the efficacy of ESAs (epoetin alfa and darbepoetin alfa) was initially established in anemic patients with chronic renal failure on dialysis. These agents have been extensively evaluated in cancer patients. While numerous randomized trials demonstrate that ESAs decrease the frequency of RBC transfusion in patients receiving chemotherapy for a nonmyeloid cancer, their impact on fatigue has been more difficult to demonstrate due to the direct mediating effect of hemoglobin levels and the confounding effect of transfusions. However, the available data suggest that ESAs modestly improve symptoms of fatigue in anemic patients receiving chemotherapy.Four trials of darbepoetin in anemic cancer patients (three chemotherapy-related, one not chemotherapy-related) showed a borderline statistically significant improvement in fatigue score relative to placebo (SMD in fatigue score -0.13, 95% CI -0.27 to 0.00, p = 0.05). The impact of darbepoetin on cancer-related fatigue was further addressed in a compilation of data from the three placebo-

controlled trials of patients receiving chemotherapy for lung cancer (two trials, 595 and 314 patients each) or a lymphoproliferative malignancy (one trial, 349 patients) [32]. Fatigue was measured using the FACT-F scale.

Until recently, ESAs were heavily promoted and utilized in cancer patients who had fatigue and any degree of anemia, whether related to chemotherapy or not. However, use of these agents has become controversial, particularly in patients with anemia unrelated to chemotherapy and in those receiving myelosuppressive chemotherapy with the intent of cure, because of concerns about thromboembolic side effects, higher mortality rates, and the possibility of adverse cancer outcomes.

At least eight trials have shown inferior survival, worse locoregional tumor control, and/or increased risk of thromboemboli in solid tumor patients treated with ESAs. In all eight, ESA dosing was targeted to achieve and maintain hemoglobin levels in excess of current recommendations (≥ 12 g/dL); in four, patients were receiving adjuvant or neoadjuvant chemotherapy for a potentially curable cancer, and in three, ESAs were administered to patients not receiving chemotherapy. These data led the US Food and Drug Administration to mandate labeling changes for ESAs that state that they are not indicated in patients with non-chemotherapy-related anemia or for those receiving myelosuppressive chemotherapy when the anticipated outcome is cure. The risks of shortened survival and inferior tumor control have neither been excluded nor confirmed when ESAs are dosed to a target hemoglobin <12 g/dL, the

level supported by ASCO/ASH and NCCN guidelines . Nevertheless, all three groups recommend that ESAs NOT be used for cancer patients with anemia not associated with chemotherapy, that ESAs not be instituted unless the hemoglobin level is ≤ 10 g/dL, and that target hemoglobin levels not exceed 12 g/dL [33] .

The above data relate to patients being treated for a nonmyeloid malignancy. The use of ESAs in patients with hematologic neoplasms is more complex. Although thromboembolic events and adverse cancer outcomes have not been reported, there is less evidence to support benefit from ESAs, responsiveness of the bone marrow may be compromised in these settings, and there are persisting concerns as to the possibility of stimulating clonal growth with hematopoietic growth factors.

Cognitive-behavioral and psychosocial interventions — Ideally, information about the expected pattern and duration of fatigue should be offered to patients before they start treatment with chemotherapy, high-risk molecularly-targeted compounds, radiation therapy (RT), or biologic response modifiers. Randomized trials and a meta-analysis indicate that a variety of nonpharmacologic psychoeducation interventions are effective for improving cancer-related fatigue[34,35,36,37,38,39], and its benefits have been shown to persist for at least two years after intervention . However, whether all patients require formal cognitive behavioral therapy (CBT) by a psychologist or psychiatrist is unclear.

The benefit of a defined program of energy conservation and activity management (ECAM) was shown in a trial in which 396 cancer patients beginning chemotherapy, radiation, or both were randomly assigned to a semistructured, customized ECAM intervention (focusing on specific strategies and methods to conserve energy) administered by nurses or a control group, for whom a similar amount of nursing time and attention was focused on diet and nutrition . Individuals who received the ECAM intervention had a significantly greater decrease in fatigue over time compared to the control group; however, this did not translate into improved overall functional performance.

To the extent that fatigue has a physiologic basis, cognitive-behavioral interventions may not be effective in all patients. In a randomized study that included 115 patients receiving radiation therapy for advanced cancer, a structured multidisciplinary program that included cognitive, emotional, physical, social, and spiritual interventions did not prevent the development of fatigue [39] , even though it was associated with an improvement in quality of life [40].

The challenge to the practitioner is to match the characteristics of individual patients with the most helpful and cost-effective interventions.

Exercise — To avoid fatigue, cancer patients often are advised to rest and downregulate their daily activities. However, because inactivity can induce muscular wasting, prolonged rest can lead to further loss of physical strength and endurance[41]. Although many fatigued patients have difficulty believing that exercise will improve their symptoms, physical exercise training programs can increase functional capacity, leading to reduced effort in performing usual activities and a decreased sense of fatigue[42,43].

Research on the effects of exercise on cancer-related fatigue includes studies of patients receiving active treatment and those who have completed treatment. Experimental designs vary, sample sizes often are small, and many series are limited to women with breast cancer. The type of aerobic exercise is variable, with some studies evaluating walking, bicycling, resistance training , or a combined approach , and still others where the patient was allowed to choose the type of exercise he or she preferred . The recommended exercise programs vary in length from six weeks to six months.

Regardless of these limitations, all studies, as well as three comprehensive reviews on the benefits of exercise in patients with cancer[44,45], demonstrate significant benefits for moderate exercise in patients with cancer. Patients who exercise during or after the

completion of treatment have significantly less fatigue and emotional distress, decreased sleep disturbance, improved functional capacity, and better QOL compared to those who do not.

Sleep therapy — Sleep disturbance associated with fatigue is often difficult to treat and manage. It may be influenced by numerous factors including daytime naps, depression, anxiety, medication, sleep interruption because of nocturia or hot flashes, and evening food and/or beverage intake.

Although sleep disturbance is common in patients with cancer, few studies have evaluated sleep interventions to manage fatigue: In a pilot study of 25 women receiving adjuvant chemotherapy for breast cancer, stimulus control (ie, having a consistent time to lie down and get up, avoiding caffeine and stimulating activity in the evening) and sleep restriction (ie, avoiding long or late-afternoon naps, limiting time in bed to the normal hours of sleep only) significantly improved fatigue[46]. Benefit from a multimodality sleep hygiene program was suggested in a controlled study of two different relaxation techniques for up to six months[47]. Compared to the control group, both intervention groups had significantly better sleep latency, sleep duration, and daytime functioning.

Acupuncture — A possible benefit from acupuncture was suggested in a randomized phase II trial involving 37 patients who had persisting fatigue but no severe

depression or anemia after completing chemotherapy an average of more than two years previously.

These data are insufficient to conclude that there is benefit from acupuncture. Further studies in larger cohorts are needed.

Pharmacologic management — Although empiric administration of psycho stimulants in patients with cancer-related fatigue has been reported to improve symptoms in open-label studies, double-blinded trials are needed to prove benefit in view of the subjective nature of fatigue and the demonstrated therapeutic effect from placebo in at least one double-blind trial .

Methylphenidate — Methylphenidate, a central nervous system stimulant that is structurally related to amphetamines, has a short half-life and a rapid onset of action. Open-label studies suggested an improvement in symptoms of fatigue, sedation, and pain[48].

Modafinil — Modafinil, a non-amphetamine "wake-promoting agent", is used for the treatment of narcolepsy. Limited experience in cancer patients suggests that modafinil is well tolerated and may be a useful treatment for cancer-related fatigue, particularly in patients with severe fatigue. The benefits of modafinil in the treatment of cancer-

related fatigue can be illustrated by the following data: In a pilot study presented at the ASCO meeting in June 2006, 30 patients with primary brain tumors complicated by neurobehavioral dysfunction and fatigue were randomly assigned to modafinil at either 200 or 400 mg/day for three weeks[49]. This was followed by a washout period of one week and open label extension of treatment for an additional eight weeks. Analysis of neurobehavioral function and fatigue demonstrated improvement across cognitive, mood, and fatigue outcome measures, with the maximum benefit at eight weeks after initiation of treatment. In a preliminary report at the 2008 ASCO meeting, patients receiving modafinil rather than placebo had a significant overall benefit from the drug as assessed by self-report of symptoms during cycle four of therapy; however, the benefit seemed to be limited to those with severe fatigue (>6 on a 10-point scale). Modafinil did not improve depression, reinforcing the view that depression and cancer-related fatigue are not linked.

Starting doses of modafinil are usually 100 to 200 mg in the morning and again at noon. The maximum daily dose is 400 mg.

Antidepressants — At least three placebo-controlled, randomized trials in patients undergoing cancer treatment have failed to demonstrate any improvement in fatigue in

patients randomly assigned to receive an antidepressant (paroxetine, sertraline), despite improvement in depressive symptoms.

However, antidepressants may be helpful when a patient has both fatigue and depression. For patients who also have insomnia, nortriptyline or amitriptyline are good choices. Case reports suggest efficacy for bupropion in patients with chronic fatigue syndrome, but no data are available in patients with cancer-related fatigue.

Steroids — Anecdotal experience suggests that corticosteroids may be beneficial for some patients with cancer-related fatigue[50]; however, side effects limit their long-term use. Steroids may be most helpful for patients with cancer-related fatigue who are in the terminal phase of advanced cancer. Dose management is improtant, as this class of drugs may induce insomnia and/or behavioral changes.

Donepezil — Pilot studies with donepezil, a selective acetylcholinesterase inhibitor, suggested that this approach might be useful in patients with cancer-related fatigue. However, a randomized trial did not show any benefit compared to placebo[51].

Multivitamins — Multivitamins have been assessed in a small randomized trial, in an effort to ameliorate the fatigue in women receiving radiation therapy. No benefit could be ascribed to the use of multivitamins.

As we can see from the above discussion there is no one single or for that matter multi-dimensional treatment modality that is effective in treating the Cancer Related Fatigue.

Perhaps the answers will be found only when effective questions are asked.

This study was an effort to prove the prevalence of this debilitating symptom that every cancer patient complains of during the course of the disease.

We sincerely hope that the effective methods like the Fatigue scale & the FACT-G questionnaires find their way into daily practice so that Fatigue can be screened effectively & every effort can be made to decrease the fatigue & improve the Quality of life in Cancer Patients.

This study concludes that Cancer Related Fatigue is real & it effects Quality of Life of patients , so the vital question is

Will improvement in quality of life (QOL) impact fatigue in patients receiving treatment for cancer?

The answer to the above question needs to be studied further.

CONCLUSION

Fatigue prevalence – In this study 100% of the patients studied had fatigue be it either mild, moderate or severe. While other studies have had ranges from 65-90%.One of the reasons for this variation could be that the patients in this study were all from low socio-economic group which makes it that much harder for them to have nutritious wholesome meal for 3/day.

Cancer Related Fatigue affected all areas of patient's life. Cancer related fatigue effected the time taken by the patients to attain normal productive life

Cancer Related Fatigue peaked at 4-5 weeks of treatment .As observed in this study & review of the previous literature suggests that the Cancer related fatigue peaked during 4^{th}- 5^{th} week of the treatment .The reason for this needs to be further evaluated.

Cancer Related Fatigue reduces the Quality of Life in patients .Cancer related fatigue effected every aspect of the patients life. It had a negative effect on the Emotional, Functional, Physical & social well being of the patients.

Cancer related fatigue never reached pretreatment level scores. In this study none of the patients ever reported to reach the pre-treatment levels of fatigue even at 2 months of follow up.

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APPENDIX XI - FACT-G Scoring Guidelines (Version 4)

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total FACT-G score. ***The higher the score, the better the QOL.***

Subscale	Item Code	Reverse item?	Item response	Item Score
PHYSICAL WELLBEING (PWB)	GP1	4	- _____	=_____
	GP2	4	- _____	=_____
	GP3	4	- _____	=_____
	GP4	4	- _____	=_____
Score range: 0-28	GP5	4	- _____	=_____
	GP6	4	- _____	=_____
	GP7	4	- _____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY WELLBEING (SWB)	GS1	0	+ _____	=_____
	GS2	0	+ _____	=_____
	GS3	0	+ _____	=_____
	GS4	0	+ _____	=_____
Score range: 0-28	GS5	0	+ _____	=_____
	GS6	0	+ _____	=_____
	GS7	0	+ _____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**SWB subscale score**

EMOTIONAL WELLBEING (EWB)	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____=**EWB subscale score**

FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**FWB subscale score**

TOTAL SCORE:

Score range: 0-108

_____ + _____ + _____ + _____=_____=**FACT-G Total score**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

*For additional guidelines please refer to the Administration and Scoring Guidelines in the manual or at www.facit.org.