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The Consequences of Fatigue in Patients Diagnosed with Hepatobiliary Carcinoma

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Running Head: Fatigue and HBC

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Abstract

Background: Fatigue is one of the most common and distressing symptoms of patients diagnosed with cancer. However, few treatments have been developed to alleviate the symptoms of cancer-related fatigue. The aims of the present study were to prospectively (1) assess the prevalence of fatigue in patients diagnosed with hepatobiliary carcinoma, (2) evaluate the relationship among fatigue, depression, sleep, and pain, (3) examine the relationship between fatigue and biological factors while covarying for potential contributing psychological and biological factors in patients diagnosed with hepatobiliary carcinoma.

Method: One hundred and one patients diagnosed with hepatobiliary carcinoma were administered a battery of questionnaires that included the Functional Assessment of Cancer Therapy-Hepatobiliary and Fatigue modules as well as the Center for Epidemiological Studies-Depression scale prior to the initiation of treatment and at 2- and 4-months post-treatment. Granulocyte colony stimulating factor (G-CSF), white and red blood cell counts, hemoglobin levels and cytokine levels were measured in the patients' sera at approximately the same time points as fatigue. Descriptive statistics, trajectory analyses and non-parametric analyses were employed to examine the relationships among variables.

Results: Nearly 100% of the patients included in the study reported symptoms of fatigue. Fatigue was significantly associated with depression at baseline ($p < 0.001$), two months ($p = 0.02$), and four months ($p=0.003$). Pain ($r = 0.403$, $p = 0.02$) and sleep ($r = -0.29$, $p = 0.02$) were both associated with fatigue at baseline but not at two months or four months. Prior to treatment, there was a trend towards significance for the association between fatigue and abnormal levels of GCSF (Mann-Whitney $U = 454.5$, $p = 0.061$). Fatigue was significantly associated with abnormal levels GCSF at both two months (Mann-Whitney $U = 49.0$, $p = 0.009$) and four months (Mann-Whitney $U = 4.00$, $p = 0.008$).

Conclusions: Consistent with prior research, fatigue is associated with decreased quality of life, depressive symptoms, sleep, and pain. The association between fatigue and abnormal levels of GCSF may be important as treatments are considered for patients experiencing symptoms of cancer-related fatigue.

The Consequences of Fatigue in Patients Diagnosed with Hepatobiliary Carcinoma

Fatigue is the most prevalent and the most distressing symptom experienced by patients diagnosed with cancer (Stasi et al, 2003). It has been estimated that 24% of cancer patients experience fatigue prior to treatment (Goedendorp et al, 2008) and another 80% report symptoms of fatigue following treatment (Theobald, 2004). The prevalence of fatigue also varies among different cancer types (NIH Consensus Statement). Patients diagnosed with gastrointestinal cancer have been reported to have symptoms of fatigue most frequently when compared to patients diagnosed with other cancer types (Goedendorp et al, 2008).

The prevalence of fatigue underscores the importance of investigating further its contributing factors and potential treatment options. The identification of such predictors and its treatments is difficult because the symptoms of cancer-related fatigue differ from the symptoms of fatigue in healthy individuals (Morrow et al, 2002). Specifically, cancer-related fatigue cannot be alleviated through restful sleep (Hofman et al, 2007). Nonetheless, several factors, including both biological and psychological, have been proposed that may contribute to the development of cancer-related fatigue. The psychosocial etiologies include distress or depression (Seo et al, 2009), pain, and sleep disturbances (Mock et al, 2000). The biological factors include lower levels of red (Mock et al, 2000) and white blood cells, cytokine dysregulation, lower hemoglobin levels, cancer-related treatments (Barnes & Bruera, 2002), and disease status (Armstrong et al, 2010).

Depression (Kuhnt et al, 2009), sleep, and pain (Brown and Kroenke, 2009; Donovan and Jacobsen, 2007) are the psychosocial predictors of fatigue that have consistently been shown to be associated symptoms of cancer related fatigue. Studies have demonstrated that the symptoms of depression and the symptoms of fatigue often overlap in cancer patients (Jacobsen et al, 2003). A recent study of multiple cancer types found that the 12% of cancer patients experience both symptoms of depression and symptoms of fatigue (dos Santos et al, 2009). Recent studies have sought to identify potential variables that mediate the relationship between depression and fatigue. Such mediating variables may include an inability to sleep (Stepanski et al, 2009) and the perception that fatigue interferes with daily activities (Barsevick et al, 2006). Research has demonstrated that sleep is also an independent predictor of cancer related fatigue (Banthia et al, 2009). A recent study also suggests pain is the second most prevalent side effect of cancer and is significantly associated with symptoms of fatigue (Hoffman et al, 2007).

Biological predictors of fatigue, most especially with regards to anemia and hemoglobin, have been investigated further in patients diagnosed with cancer. A study of patients diagnosed with colorectal cancer, lung cancer, or ovarian cancer demonstrated a correlation between increased symptoms of fatigue and abnormally low levels of hemoglobin, especially during chemotherapy (Holzner et al, 2002). Significantly, reduced levels of hemoglobin have also been demonstrated to be associated with poorer survival in patients undergoing chemotherapy treatments (Bahl et al, 2010). Anemia results from a reduction in the number of red blood cells and has been reported in nearly 50% of patients diagnosed with cancer. The increased prevalence of anemia in cancer patients

can be attributed to the treatments these patients undergo for their cancer. Research has also demonstrated that anemia is associated with symptoms of fatigue and poorer quality of life (Gordon, 2002). Furthermore, anemia has been demonstrated to be associated with overall survival. Patients undergoing regional chemotherapy, including patients diagnosed with hepatobiliary carcinoma, have lower rates of anemia secondary to the targeted type of chemotherapy they receive in contrast to systemic chemotherapy that most patients undergo.

Recent studies have also investigated the role of pro-inflammatory cytokines with regards to the development of fatigue. Bower and colleagues have demonstrated that the increased activity of proinflammatory cytokines exacerbated the symptoms of fatigue in breast cancer and prostate cancer patients during radiation treatments (Bower et al, 2009). Furthermore, increased activity of proinflammatory cytokines was also found to be associated with fatigue that persisted following treatment (Ganz & Bower, 2007). Bower and colleagues suggest that the increased activity of cytokines may result from decreased glucocorticoid response to stress (Bower et al, 2007). Orre and colleagues demonstrated that chronic fatigue in patients diagnosed with testicular cancer was associated with elevated levels of the IL-1 cytokine and C-reactive protein (Orre et al, 2009).

The psychosocial and biological predictors of cancer-related fatigue warrant further research because the relationship between fatigue and quality of life has been demonstrated to be significant (So et al, 2009). Fatigue has been demonstrated to be symptom that most adversely affects a patient's quality of life (van den Beuken, et al, 2009), especially following surgical procedures (Rutegard et al, 2009). Further investigation of the predictors of fatigue is also warranted in order to facilitate the

development of treatment options, which are currently limited (Escalante & Manzullo, 2009). Stimulants including modafinil and methylphenidate have recently been studied as potential pharmacological interventions that may reduce the symptoms of cancer-related fatigue (Escalante & Manzullo, 2009). A recent meta-analysis evaluated the efficacy of non-pharmacological interventions as prospective treatments for the symptoms of cancer-related fatigue. The study found that non-pharmacological interventions including psychosocial interventions and exercise were successful in the reduction of the symptoms of cancer-related fatigue (Kangas et al, 2009). Behavioral therapy has also been demonstrated to improve sleep quality, which may be effective in the reduction of cancer-related fatigue (Berger et al, 2009). It is likely that cancer-related fatigue has multiple etiologies. Therefore, it is important to understand the psychological and biological predictors of fatigue in order to develop appropriate treatments.

The present study sought to investigate further the psychological and biological mechanisms underlying the symptoms of cancer-related fatigue, in patients diagnosed with hepatobilary carcinoma. Specifically, the study will investigate the role of several immune parameters including cytokines and granulocyte colony stimulating factor (GCSF). GCSF is a cytokine that stimulates the production of neutrophils. Synthetic GCSF (e.g. Neupogen) is often used to increase the white blood cell count in patients undergoing treatment for chemotherapy (Neupogen Product Information). The present study is unique in that it will also evaluate the relationship between these immune parameters and the factors influencing the development of fatigue including depression, sleep, pain, hemoglobin levels, and red and white blood cell counts. The investigation of the associations between these variables and fatigue will enhance the results regarding the

associations between fatigue and various immune parameters because these extraneous variables will be eliminated as possible factors contributing to the associations between fatigue and immune parameters. The primary aims of the present study are to (1) assess the prevalence of fatigue in patients diagnosed with hepatobiliary and the effect of fatigue on quality of life (2) evaluate the relationship among fatigue, depression, sleep and pain in patients diagnosed with hepatobiliary carcinoma, (3) examine the relationship between fatigue and biological factors while covarying for potential psychological and biological factors that may contribute to the development of fatigue in patients diagnosed with hepatobiliary carcinoma.

Methods

Participants

One hundred and one patients diagnosed with biopsy-proven hepatobiliary carcinoma were recruited from the University of Pittsburgh Medical Center between January 2007 and October 2009. Patient inclusion criteria were (1) biopsy, radiological, and/or biological evidence of hepatobiliary carcinoma (2) age 18 years or older and (3) fluency in English. Exclusion criteria included the (1) presence of suicidal or homicidal ideation, or (2) current psychosis or thought disorder.

Instruments

Sociodemographic and Disease Specific Factors

Sociodemographic and disease specific information was collected from medical records. The medical team followed patients until death or loss to follow-up. If the patient was lost to follow-up, the patient's date of death was obtained through the Social Security Death Index.

Depression

The CES-D is a 20-item self-report questionnaire and provides an index for the presence of depressive symptoms. The items of the questionnaire inquire about depressive symptoms in the previous seven days. Participants respond to such queries on a four-point Likert scale (0 = rarely or none of the time; 1 = some or a little of the time; 2 = occasionally or a moderate amount of time; and 3 = most or all of the time). The established clinical cutoff is a score of 16, which reflects clinical levels of depression. The CES-D has demonstrated adequate construct validity and was found to be reliable in studies including patients with breast cancer (Okun et al, 1996; Hann et al, 1999).

FACT-An

The Functional Assessment of Cancer Therapy - Anemia (FACT-AN) is a 20-item questionnaire comprised of two subscales: a 13-item Fatigue subscale and a 7-item non-fatigue Anemia subscale. The 13-item Fatigue subscale of the FACT-F independently demonstrated good test–retest reliability (r = 0.90), internal consistency (alphas = 0.93 and 0.95) on initial and test-retest administrations, suggesting an ability to be used as an independent, brief, unidimensional measure of fatigue. These subscales address the implications or consequences of fatigue in addition to symptom expression and have important implications for overall quality of life in patients diagnosed with cancer (Yellen & Cella, 1997).

Brief Pain Inventory

The Brief Pain Inventory (BPI) is a pain assessment tool for use with cancer patients. The BPI measures both the intensity of pain (sensory dimension) and the interference of pain in the patient's life (reactive dimension). It also queries about pain

relief, pain quality, and patient perception of the cause of pain. The BPI has demonstrated both reliability and validity across cultures and languages (Cleeland & Ryan 1994).

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score. Clinical and clinimetric properties of the PSQI were assessed over an 18-month period with "good" sleepers (healthy subjects, n = 52) and "poor" sleepers (depressed patients, n = 54; sleep-disorder patients, n = 62). Acceptable measures of internal homogeneity, consistency (test-retest reliability), and validity were obtained. A global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% (kappa = 0.75, $p < 0.001$) in distinguishing good and poor sleepers. The clinimetric and clinical properties of the PSQI suggest its utility both in psychiatric clinical practice and research activities (Buysse & Reynolds, 1989).

Health Related Quality of Life

The Functional Assessment of Cancer Therapy (FACT-Hep) was used to assess changes in symptoms and side effects of treatment. The FACT-Hep includes both the FACT-General (a 27-item instrument that measures four dimensions of quality of life) and a module with 18 items specific to hepatobiliary disease (26). The FACT-G has four subscales for physical (PWB), social and family (SFWB), emotional (EWB), and functional well-being (FWB). The hepatobiliary module (FACT-Hep) includes items that

pertain to symptoms of the disease as well as side effects of the treatment. The FACT is one of the most widely utilized quality of life questionnaires in clinical trials for new cancer treatments, and both the FACT-G and the FACT-Hep has been demonstrated to be a valid and reliable instrument (Heffernan et al, 2002).

Biological Parameters

The red and white blood cell counts, neutrophil levels, and hemoglobin levels of the patients included in the study were measured at baseline and every two months, as a subset of the routine laboratory testing. Immune assays that were conducted to assess $CD56^{+}$ / CD16, NK cell number and activity, and serum cytokine levels (IL-1, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, GCSF, IL-22, IL-23, IFN-g, and TNF-a). The assays were performed at the University of Pittsburgh Cancer Institute's lab. The blood draws were performed between the hours of 8:00 a.m. and 12:00 p.m. to control for differences in circadian rhythms on proposed immune system parameters. The University of Pittsburgh Cancer Institute laboratory uses standardized and validated assays, standard operating procedures and biostatistical input, which reduces concerns regarding lab-based variations. The absolute number and the percentage of NK cells ($CD3^{-}$, $CD56^{+}$, and CD16) were determined by a single-platform flow cytometry-based method. Whole blood was used for staining of NK cells with fluorochrome-labeled monoclonal antibodies. Following lysis of the erythrocytes and the addition of sizing beads, NK cells were enumerated in a Coulter flow cytometer.

Procedure

Before the study commenced, Institutional Review Board approval was given. Patients provided written informed consent prior to their participation. Upon receiving

written consent, patients were administered a battery of questionnaires by a clinical psychologist before the initiation of treatment. The patients completed the same battery of questionnaires every two months during the first year and every six months during the second year. Blood draws were performed at the same time as the psychosocial assessment. Unlike prior research, clinically meaningful levels of psychological (clinical range of depression) and biological parameters (abnormal levels) were employed as these are though to have an impact on health and disease.

Data Analysis

The data were analyzed using SPSS, version 16. Descriptive statistics were performed to describe sociodemographic and disease-specific characteristics of the sample. Descriptive statistics, trajectory analyses, and non-parametric analyses (Mann-Whitney U tests) were used to analyze the relationships among the variables. Specifically, the Pearson correlation coefficient was used to evaluate the associations among fatigue, depression, pain, sleep, and quality of life.

Results

Sociodemographic and Disease-Specific Factors for the Sample

Table 1 outlines the sociodemographic and disease - specific variables of the sample. The mean age of the sample was 63 years. Seventy – two percent of those who participated in the study were male, which is consistent with the 2:1 male: female ratio observed in patients diagnosed with hepatobilary carcinoma. 68% of the participants had been diagnosed with hepatocellular carcinoma as their primary cancer type. Analyses by diagnosis demonstrated that there were no significant differences among the varying diagnoses.

Prevalence of the Variables in the Sample

A trajectory analysis was performed to assess the prevalence of fatigue in the sample. Nearly 100% of the participants reported experiencing symptoms of fatigue across each time point. Furthermore, 36% of the participants reported symptoms of profound fatigue (Figure 1). Fatigue was also found to be significantly associated with overall quality of life at baseline, two months, and four months ($r = -0.62 – 0.77$, $p = 0.001$).

Associations among Fatigue and Psychosocial Factors

Fatigue was found to be significantly associated with depression at baseline ($p < 0.001$), two months ($p = 0.02$) and four months ($p = 0.003$). Pain ($r = .403$, $p = 0.02$), and sleep ($r = -0.29$, $p = .02$) were both associated with fatigue at baseline. The patients who reported more profound symptoms of fatigue also reported greater pain at baseline (Mean Rank = 17.47) when compared to patients who reported moderate symptoms of fatigue (Mean Rank = 10.95, Mann Whitney U = 54.5).

Associations among Fatigue and Biological Markers

Fatigue was not found to be significantly associated with any proinflammatory cytokines as demonstrated through previous research. However, fatigue was found to be associated with abnormal levels of GCSF at two months (Mann-Whitney U = 49.0, $p = 0.009$) and four months (Mann-Whitney U = 4.00, $p = 0.008$). There was also a robust trend towards significance for the association between fatigue and GCSF at baseline (Mann-Whitney U = 454.5, $p = 0.06$). The correlation between fatigue and GCSF at each time point was significant when several factors associated with fatigue were controlled

including the side effects of chemotherapy, the medications to treat fatigue (i.e. Neupogen), white and red blood cell counts, neutrophil counts, and hemoglobin levels.

Associations among Psychosocial Variables and GCSF

Post-hoc analyses were performed to be certain that the psychosocial variables associated with fatigue were not associated with GCSF. These analyses demonstrated that depression, sleep, and pain were not significantly associated with GCSF. However, sleep was significantly associated with abnormal levels of the IL-5 cytokine ($p = 0.006$).

Discussion

The first objective of the present study involved an analysis of the prevalence of fatigue in patients diagnosed with hepatobiliary carcinoma. 36% of the patients enrolled in the present study experienced chronic, elevated symptoms of fatigue while 100% of the patients reported some level of fatigue throughout the course of treatment. The prevalence of fatigue in the sample is consistent with the prevalence of fatigue in other cancer types. Cella and colleagues reported that approximately 60% - 96% of patients diagnosed with cancer reported fatigue at least once during the course of their treatment for their disease (Cella, 1998). The prevalence of fatigue in patients diagnosed with hepatobiliary carcinoma may be greater than the prevalence of fatigue in other cancer types. For example, a study by Bower and colleagues found that 20% of patients diagnosed with breast cancer reported symptoms of fatigue throughout the course of their treatment (Bower, 2005). The increased prevalence of fatigue in patients diagnosed with hepatobiliary carcinoma may be attributed to the advanced nature of the disease. However, it is often difficult to compare the prevalence of fatigue across studies and different cancer types because a plethora of instruments are often used to assess the

symptoms of fatigue. In addition, the timing of the assessments of such symptoms also varies among different studies.

The present study also sought to evaluate the associations among fatigue and several common contributing factors including depression, sleep and pain. The results of the present study demonstrated that fatigue was significantly associated with depression, sleep and pain, which is consistent with the results of previous studies. The association among fatigue, depression, and pain suggests that a symptom cluster may exist. Previous studies have also demonstrated that the same symptom cluster exists (Kirkova et al, 2010). These associations underscore the importance of assessing and treating symptoms of fatigue in combination with depression, sleep, and pain. Specifically, the additional factors have significant consequences. For example, depression has been demonstrated to be associated with reduced survival in patients diagnosed with hepatobiliary carcinoma (Steel et al, 2007). Since cancer-related fatigue increases the prevalence of depressive symptoms, these symptoms must be identified and subsequently treated to prevent the impact on survival. Fatigue was also found to be associated with poor quality of life as demonstrated by previous research. The association between fatigue and poor quality of life further emphasizes the importance of identifying and treating the symptoms of fatigue. The quality of life in patients diagnosed with cancer should be maximized; therefore, symptoms of fatigue should be treated and reduced. The identification of the common psychosocial factors associated with fatigue may facilitate improvements in the assessment and treatment of the symptoms of cancer-related fatigue.

The identification of the biological factors associated with fatigue will likely also improve the assessment and treatment of cancer-related fatigue. The present study found

a significant association was found for the association between fatigue at two months and four months with abnormal levels of GCSF. However, depression, sleep and pain were not found to be associated with GCSF. The association between fatigue and the levels of GCSF was present across several points. Furthermore, the correlation was significant when several biological factors associated with fatigue were controlled including red blood cells, white blood cells, hemoglobin, cytokines including IL-2, IL-6, TNF-alpha, IFN-gamma and the number natural killer cells. Although fatigue was not found to be significantly associated various cytokines as demonstrated through previous research (Bower et al), there was a significant association between IL-5 and sleep. Importantly, sleep was also associated with fatigue. Therefore, previous studies that have demonstrated a significant association between fatigue and various cytokines may not have controlled for sleep.

There is a paucity of research regarding the association between fatigue and GCSF. However, the significant association between fatigue and GCSF across multiple time points as demonstrated in the present study suggests future investigation into the association is warranted. Specifically, the findings of the present study may suggest that the assessment of GCSF rather than the traditional measures of red and white blood cells and hemoglobin levels may be recommended as the etiology of cancer-related fatigue is identified. Future research should also investigate the treatment of cancer-related fatigue using medications that change the levels of circulating GCSF such as Neupogen. Non-pharmacological interventions such as physical activity and behavioral therapy may continue to alleviate the comorbid symptoms associated with fatigue including depression and sleep.

The present study demonstrated a significant association between GCSF and fatigue that was independent of psychological and biological etiologies of fatigue. The results of the present study may have important clinical implications as treatments for cancer-related fatigue are identified and assessed. Although the present study controlled for several psychosocial and biological variables often associated with fatigue, there were limitations of the study. First, multiple statistical comparisons were performed using a relatively small sample size; therefore, the power of the results may have been reduced. Second, the prevalence of fatigue and the associations between fatigue and several variables were evaluated in a heterogeneous population of cancer patients. While the majority of the patients presented with hepatocellular carcinoma, patients included in the study also had diagnoses of different primary cancer types including colorectal cancer. Nonetheless, the results of the present study warrant further investigation into the relationship between fatigue and GCSF and the potential clinical implications of the relationship.

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Table 1. Sociodemographic and Disease – Specific Characteristics of the Sample

Characteristic	**N = 100**
Age (mean)	62.5 years ± 11.7
Gender (% male)	72.3
Diagnosis (%)	
HCC	68.2
CCC	4.7
Colorectal	7.4
Other	13.5
Cirrhosis (%)	56.1
Number of Lesions (%)	
One	22.3
Two	18.2
Three	8.8
Four	2.7
Five	.7
More than Five	31.1
Vascularity (%)	
Hyper	53.4
Hypo	17.6
Mixed	4.1
Vascular Invasion (%)	25.0

Figure 1. Trajectory Analysis of Fatigue