Background: To understand the pathogenesis of fatigue in cancer, we conducted a cross-sectional study using Brief Fatigue Inventory (BFI) and Functional Assessment of Cancer Therapy-Fatigue (FACT-F) instruments to measure fatigue and assessed laboratory studies.

Patients and methods: 174 patients with cancer, who had undergone treatment within the last six months, answered the questionnaires and the Brief Version Zung Self-Rating Depression Scale (BZSDS). Blood samples were drawn for hemoglobin, albumin, thyroid stimulating hormone (TSH), dehydroepiandrosterone-sulfate (DHEAS) and tumor necrosis factor-alpha (TNF- alpha). Testosterone levels were checked in male patients.

Results: Clinically significant fatigue with BFI ≥4 was present in 52.0% of patients. Measurement of laboratory parameters revealed the following: DHEAS levels <80 mcg/dl in males and <36 mcg/dl in females = 54.1%; BZSDS scores ≥27 = 20.1%; testosterone levels <200 ng/dl = 26.4% of male patients. Significant correlations were noted between BFI and FACT-F, albumin levels, hemoglobin levels and BZSDS scores. In addition, for male patients BFI correlated with DHEAS and testosterone levels. In multiple linear regression, hemoglobin, BZSDS scores and current opioid use were associated with response BFI. For male patients, DHEAS <80 mcg/dl, increased BZSDS and testosterone <200 ng/dl were associated with increased BFI.

Conclusion: Fatigue is common in this population and BFI correlates with more extensive measurements. Abnormalities such as decreased testosterone and DHEAS may lead to interventions that can be therapeutically exploited.

Key words: cancer, dehydroepiandrosterone, fatigue, testosterone

Introduction

Fatigue is one of the most common and distressing symptoms reported by cancer patients. Many studies show fatigue affecting >75% of patients, especially in the setting of chemotherapy administration and radiation treatments [1, 2]. Up to 60% of patients report this as the symptom most affecting everyday life, but only a minority of patients are diagnosed and even fewer are actually offered management suggestions [3, 4].

The pathogenesis of fatigue is not well understood. It has been correlated with anemia, psychological distress, nausea, dyspnea, hypoalbuminemia, disease burden, performance status and treatment modalities [5–7]. Studies on biological correlates are very limited. Commonly checked laboratory parameters such as albumin and hemoglobin have been associated with fatigue. Anemia has been shown to be a major contributor to increased fatigue and declining quality of life in cancer populations [8]. Treatment with epoietin-α has been shown to have positive impact on activity and energy levels in these patients [9, 10]. The role of depression in causing cancer fatigue is not very clear. The two are associated and commonly coexist [11, 12].

Other promising biological markers associated with fatigue which may have a role in pathogenesis include tumor necrosis factor-α (TNF-α), hypothyroidism, dehydroepiandrosterone sulfate (DHEAS) and serum testosterone. TNF-α has been correlated with fatigue in non-cancer settings such as post-dialysis, chronic fatigue syndrome and parvovirus infections [13–15]. Higher levels of soluble TNF receptor II have been associated with fatigue in breast cancer survivors [12]. Anti-TNF therapy in a pilot study in patients with myelofibrosis with myeloid metaplasia helped relieve constitutional symptoms [16].
DHEAS and testosterone have been implicated as potential biomarkers of fatigue in HIV populations and in Addison’s disease [17, 18]. The pathophysiologic mechanisms by which these biomarkers are associated with fatigue are not clear. Also, their role in cancer-related fatigue is not defined.

In this study we evaluated the prevalence of fatigue in a diverse cancer patient population undergoing chemotherapy. We used broad entry criteria to assist with time and resource constraints, and also because we were looking for potential markers which cross different subgroups since the problem is so prevalent. Patients were screened for anemia, depression, hypoalbuminemia, hypothyroidism and TNF-α levels, and for low levels of DHEAS and total testosterone. We used this exploratory study to test the association of these parameters with clinical fatigue. In addition, we were interested in generating hypotheses based on the findings that may have therapeutic implications.

**Patients and methods**

**Sample**

This cross-sectional study was conducted at the Indiana University Medical Center and all procedures followed were in accordance with and approved by its Institutional Review Board. Patients were recruited in the outpatient clinics of the Indiana Cancer Pavilion. Patients were eligible if they were at least 18 years old with a pathological diagnosis of cancer. Patients had to have either metastatic cancer or have received chemotherapy, radiation therapy or hormonal therapy within the previous 6 months. All patients provided informed consent.

Patients with prostate cancer were excluded since androgen levels were being screened, as were patients who were unable to give informed consent or to read and understand the self-reported questionnaires in English.

**Data collection and study parameters**

Information on the patient’s disease, treatments, current medications and performance status was collected by a research nurse. Disease data included diagnosis, site and stage of disease. The Brief Fatigue Inventory (BFI), the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) questionnaires and the Brief Zung Self-Reporting Depression Scale (BZSDS) were administered to all the patients. At the same visit, blood samples were drawn for determining hemoglobin, albumin, total testosterone levels, DHEAS, thyroid-stimulating hormone (TSH) and TNF-α levels.

The BFI is a nine-item questionnaire that checks the patient’s subjective report of fatigue severity. Patients rate each item based on how they feel currently and in the preceding week, using a 0–10 numerical scale. The mean of the nine items gives the total BFI score. The score is categorized as mild (0–3), moderate (4–6) or severe (7–10). It is a reliable (internally stable) test with low measurement error (α = 0.96) [19]. BFI scores have been validated to results of the more detailed FACT-F scales in the past. Because of its abbreviated format, we opted to use BFI to screen for prevalence in order to reduce the burden on patients. FACT-F has been studied much more extensively as a fatigue measurement tool and is comprised of the FACT-General and the FACIT-F scale [20, 21]. FACT-General is a 33-item self-administered questionnaire covering the quality-of-life domains of physical, social, emotional and functional well-being, and the FACIT-F is a 13-item subscale which covers specific fatigue questions. Patients report their answers on a five-point scale for how true statements describe them in the past 7 days. After accounting for reverse-scored items, questions are summed across the subscales and added for a total score, with higher scores indicative of greater overall quality of life. We have incorporated FACT-F in clinical studies at our institution to serve as an alternative tool to BFI.

The BZSDS self-administered depression scale was developed from the widely used Zung Self-Rating Depression Scale [22]. It is an 11-item questionnaire focusing on depression. The sum of the 11 items, after correcting for the seven reverse-scored items, is converted into a score. Patients can be subdivided into groups based on the severity of their depressive symptoms. The different categories used based on the BZSDS scores are normal (0–21), mild depression (22–26), moderate depression (27–30) and severe depression (≥31).

Data on performance status of the patients was collected using the Eastern Cooperative Group (ECOG) scales from 0 to 4. A score of 0 represented fully active predisease performance without restriction, a score of 1 represented ability to carry out light or sedentary work and a score of 2 reflected ability to perform self-care but not any work. A score of 3 reflected only limited self-care ability and confinement to bed or chair for >50% of waking hours, while a score of 4 represented complete disability and total confinement to bed or chair.

**Laboratory tests and cytokine analysis**

TNF-α levels were determined using commercially available Quantikine Immunoassay kits (R&D Systems Inc., Minneapolis, MN). The blood samples were immediately frozen at temperatures below −20°C and the measurements were carried out according to the instructions of the manufacturer. The reference values for TNF-α for healthy volunteers were <4.71 pg/ml as quoted by the manufacturer. The intra-assay precision as reported by the manufacturer was tested in three samples of known concentration in replicates of 20. The CV% ranged from 8.8 to 5.3. The inter-assay precision in three samples of known concentration as evaluated in 40 separate assays had a CV% range of 16.7–10.8.

Other reference values used included hemoglobin <11 g/dl to define anemia for both males and females. This was believed to be a clinically useful cut-off as suggested by some studies [23, 24] The Indiana University laboratory reference values were used to define albumin <3.5 g/dl as low and TSH was considered high if it was greater than the laboratory reference value of 4.2 μ U/ml. DHEAS levels were considered low if they were <80 μg/dl in males or <36 μg/dl in females (our laboratory reference values). Total testosterone levels were checked in male patients and values <200 ng/dl were considered low.

**Statistical analysis**

A total of 175 patients were to be accrued to provide a sample size with >90% power by regression analysis and with a 5% significance level to detect a correlation of 0.25 between a covariate and a dependent variable. Pearson’s correlation coefficients were calculated for continuous data. We present correlation between BFI and FACT-F to show the degree to which the scales are related in this sample. Multiple linear regression analysis was used to test the association between the response variable BFI (scale 0–10) and multiple predictors. Statistical tests were two-sided at the 0.05 significance level. Analyses were performed using SAS version 8.02.

**Results**

**Sample characteristics**

A total of 175 patients were enrolled. One patient did not complete the questionnaire and was excluded. All the remaining 174 patients completed the study assessments and were...
included in the analysis. The median age was 58 years. Most patients (92.0%) had an ECOG performance status of 0 or 1. The most common primary site of disease was the lung (41.4%), followed by breast (19.0%) and lymphoma (18.4%). A total of 168 patients had received chemotherapy in the preceding 6 months and 118 of these had received chemotherapy within the preceding 4 weeks. Twenty-four patients had received radiation therapy in the preceding 6 months and six of these had received it in the 4 weeks before the survey. Table 1 lists the characteristics of the sample population.

### Table 1. Sample characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study patients</td>
<td>174 (100)</td>
</tr>
<tr>
<td>Males</td>
<td>87 (50)</td>
</tr>
<tr>
<td>Females</td>
<td>87 (50)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>58 years</td>
</tr>
<tr>
<td>Range</td>
<td>20–83 years</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>93 (53.5)</td>
</tr>
<tr>
<td>1</td>
<td>67 (38.5)</td>
</tr>
<tr>
<td>2</td>
<td>11 (6.3)</td>
</tr>
<tr>
<td>3</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Primary disease site</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>72 (41.4)</td>
</tr>
<tr>
<td>Breast</td>
<td>33 (19.0)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>32 (18.4)</td>
</tr>
<tr>
<td>Renal</td>
<td>13 (7.5)</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td>Others</td>
<td>17 (9.8)</td>
</tr>
<tr>
<td>Treatment within the last 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>118 (67.8)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>6 (3.5)</td>
</tr>
<tr>
<td>Current opioid use</td>
<td>60 (34.5)</td>
</tr>
</tbody>
</table>

Prevalence of fatigue, depression and abnormal laboratory parameters

Moderate or severe fatigue as defined by a total BFI score ≥4 was common and prevalent in 52% of the patients. The majority of these fell in the moderate fatigue category but 20 patients (11.5%) had BFI scores of ≥7 and were categorized as experiencing severe fatigue. The prevalence of anemia was 21.5% and that of moderate–severe depression was 20.1%. Low levels of DHEAS were seen in 42.4% of females and 65.5% of males. Total testosterone levels <200 ng/dl were seen in 26.4% of males. TNF-α levels were available for only 169 patients. Abnormal laboratory parameters and results of questionnaire findings are summarized in Table 2.

### Table 2. Abnormal data parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (%)</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue prevalence (BFI ≥4)</td>
<td>91 (52.0)</td>
<td>4.4</td>
<td>2.36</td>
<td>0–10</td>
</tr>
<tr>
<td>Hypothyroidism (TSH &gt;4.2 μU/ml)</td>
<td>12 (6.9)</td>
<td>1.3</td>
<td>18.2</td>
<td>0.02–224.9</td>
</tr>
<tr>
<td>Hypoalbuminemia (albumin &lt;3.5 g/dl)</td>
<td>40 (23.1)</td>
<td>3.7</td>
<td>0.38</td>
<td>2.7–4.6</td>
</tr>
<tr>
<td>Anemia (hemoglobin &lt;11 g/dl)</td>
<td>37 (21.5)</td>
<td>12.5</td>
<td>1.6</td>
<td>7.9–15.6</td>
</tr>
<tr>
<td>Depression (BZSDS ≥ 27)</td>
<td>35 (20.1)</td>
<td>20.0</td>
<td>6.5</td>
<td>11–40</td>
</tr>
<tr>
<td>TNF-α (≥4.71 pg/ml, n = 169)</td>
<td>12 (6.9)</td>
<td>2.3</td>
<td>1.85</td>
<td>0.34–12.83</td>
</tr>
<tr>
<td>Low DHEAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females (&lt;36 μg/dl; n = 87)</td>
<td>36 (42.4)</td>
<td>48.0</td>
<td>52.9</td>
<td>1.3–336</td>
</tr>
<tr>
<td>Males (&lt;80 μg/dl; n = 87)</td>
<td>57 (65.5)</td>
<td>49.0</td>
<td>93.23</td>
<td>30–536</td>
</tr>
<tr>
<td>Testosterone (males &lt;200 ng/dl; n = 87)</td>
<td>23 (26.4)</td>
<td>299.0</td>
<td>208.37</td>
<td>4–982</td>
</tr>
</tbody>
</table>

Correlates of moderate to severe fatigue

BFI scores were highly correlated with FACT-F scores ($r = -0.80, P < 0.0001$) and moderately with BZSDS scores ($r = 0.54, P < 0.0001$). Since fatigue is indicated by higher scores on FACT-F and lower scores on the BFI, the scales show a high association in measurement of fatigue. BFI showed a weak negative correlation with albumin levels ($r = -0.22, P = 0.004$) and hemoglobin levels ($r = -0.28, P = 0.0002$). There were no significant correlations of BFI or FACT-F scores with TNF-α levels. There were no other significant correlations for the pooled sample with BFI ($r > 0.2$, $P < 0.05$). BFI scores for male patients had weak negative correlations with DHEAS levels ($r = -0.22, P = 0.035$) and testosterone levels ($r = -0.27, P = 0.011$).

Correlates of age were also calculated. Age was negatively correlated with albumin and DHEAS ($r = -0.30, P < 0.0001$ and $r = -0.53, P < 0.0001$, respectively). Correlations with age were similar in male and female subgroups. In addition, there was a weak negative correlation between age and testosterone in males ($r = -0.23, P = 0.032$).

Multiple linear regression analysis

Multiple linear regression analysis was used to analyze the association between BFI and factors BZSDS, TSH, albumin,
hemoglobin, time since last chemotherapy (>28 days compared with <29 days), days since last radiation therapy (>28 days compared with <29 days), current opioid use and age. In selecting these factors we used not only biological variables of interest as per the study, but also added other relevant clinical factors which were felt to be influencing fatigue. These included the timing of chemotherapy and radiation therapy with respect to the point time when BFI was measured, as well as age and the current use of opioids. The full model was reduced using stepwise elimination to include only factors with P-values <0.10. NA designates effects not appropriate for inclusion in the full or reduced model based on sample characteristics. The combined group analyses did not include factors for testosterone or DHEAS. Analyses for females did not include testosterone. Days since chemotherapy (Days chemo), days since radiation therapy (Days XRT), testosterone levels (Low testosterone) and DHEAS levels (Low DHEAS) were dichotomized and analyzed as categorical. The cut-offs used are given in the section on multiple linear regression analysis.

\[
\begin{array}{cccccccc}
\text{Low testosterone} & \text{Combined full} & \text{Combined reduced} & \text{Male full} & \text{Male 1 reduced} & \text{Male 2 reduced} & \text{Female full} & \text{Female reduced} \\
\hline
\text{Low DHEAS} & \text{NA} & \text{NA} & 0.152 & 0.031 & – & \text{NA} & \text{NA} \\
\text{BZSDS score} & <0.0001 & <0.0001 & <0.0001 & <0.0001 & <0.0001 & <0.0001 & <0.0001 \\
\text{log(TSH)} & 0.969 & – & 0.743 & – & – & 0.352 & – \\
\text{Hemoglobin} & 0.143 & 0.027 & 0.275 & – & – & 0.125 & 0.035 \\
\text{Albumin} & 0.285 & – & 0.828 & – & – & 0.683 & – \\
\text{Days chemo} & 0.220 & – & 0.636 & – & – & 0.506 & – \\
\text{Days XRT} & 0.423 & – & 0.929 & – & – & 0.103 & – \\
\text{Opioid use} & 0.033 & 0.007 & 0.338 & – & – & 0.229 & 0.052 \\
\text{Age} & 0.385 & – & 0.081 & – & – & 0.785 & –
\end{array}
\]

\[P\text{-values for each effect included are shown by sample for the full and the reduced models. The full models were reduced using stepwise elimination for model selection of factors with } P\text{-values <0.10. NA designates effects not appropriate for inclusion in the full or reduced model based on sample characteristics. The combined group analyses did not include factors for testosterone or DHEAS. Analyses for females did not include testosterone. Days since chemotherapy (Days chemo), days since radiation therapy (Days XRT), testosterone levels (Low testosterone) and DHEAS levels (Low DHEAS) were dichotomized and analyzed as categorical. The cut-offs used are given in the section on multiple linear regression analysis.}

Discussion
This cross-sectional study found fatigue to be quite prevalent in a diverse cancer outpatients population, most of whom were undergoing active chemotherapy. We used BFI, a previously validated fatigue measurement tool for screening. This served well as a rapid screening questionnaire and correlated strongly with FACT-F, a much more extensive measurement instrument. Because of its ease of use and clinical applicability, we plan to use BFI in future studies. Our study confirmed that depression, anemia and hypoalbuminemia correlate with fatigue. In addition, we saw that low levels of testosterone and DHEAS correlated with fatigue in male patients. Current use of any opioids also showed significant association with BFI in multiple regression.

The pathogenesis of fatigue has been extremely difficult to elucidate and undoubtedly reflects the multiple etiologies that contribute to its development in cancer patients. One limitation of our study is the heterogeneous population as it includes patients with different stages of solid cancers receiving adjuvant therapies, treatments for unresectable disease and metastatic disease, as well as hematological malignancies. Another obvious limitation of this study is its cross-sectional design. Symptoms of fatigue are likely to vary over the course of time and treatment. Whether the various laboratory parameters studied are epiphenomena or play roles in pathogenesis is unclear. Even for variables such as depression which have been better studied, the cause–effect relationship is not clear. In a large placebo-controlled trial conducted to look at
the effect of paroxetine on fatigue and depression in cancer patients, an effect on fatigue separate from the antidepressant effect was not found [11]. This suggested that modulation of serotonin may not be a primary mechanism of fatigue related to cancer treatment.

Some of the specific findings of the study included the association between opioid use and fatigue. Since we did not collect pain scores, it is unclear whether this is a reflection of a pain fatigue syndrome, advanced underlying disease or the use of the opioid drugs itself. In addition, chronic use of long-acting opioids has been associated with hypogonadism [25], which again points to the many potential confounding factors in studying the etiology of cancer-related fatigue.

In our present study, we generate hypotheses of correlation between fatigue and potential biological markers. Inflammatory cytokines such as TNF-α have previously been hypothesized to contribute to fatigue symptoms. Our current study failed to show any association between BFI scores and TNF-α levels in this heterogeneous population. A recent study of breast cancer patients receiving paclitaxel therapy explored the association between fatigue and influenza-like symptoms experienced by the patients and various cytokines [26]. While TNF-α levels did not correlate with the symptoms, plasma levels of interleukins 6, 8 and 10 were transiently increased with treatments and correlated with symptoms.

An important finding was that DHEAS and testosterone levels appeared to be promising markers of fatigue in male patients. It is unclear whether the finding that DHEAS was associated with fatigue in males but not in females reflect different pathophysiologic mechanisms or is confounded by other variables. For example, more females (23%) than males (17.2%) had a moderate–severe depression score on the BZSDS. Also, more females (24.7%) than males (18.4%) had a hemoglobin <11 g/dl. Low DHEAS levels have been associated with fatigue in chronic fatigue syndrome and HIV populations [18, 19]. Controlled trials in Addison’s disease have shown that DHEA supplementation helps to improve fatigue and mood [27, 28]. With respect to testosterone levels in males, most of our knowledge is based on testosterone replacement studies in non-cancer populations. Patients with known testosterone deficiency and hypogonadism have demonstrated increased muscle mass, bone mineral density, hemoglobin, sexual function and well-being with testosterone supplementation [29, 30]. Age-related decline in testicular function may occur with associated symptoms and often responds to testosterone supplementation as well. In the HIV population, testosterone treatment has been effective for the short-term treatment of symptomatic clinical hypogonadism, including low energy [31]. Very few studies have looked at its effect on cancer patients. Beneficial effects of nandrolone decanoate, an anabolic steroid, were studied in two trials of patients with advanced cancer without any exclusion criteria based on testosterone levels [32, 33]. They showed that treatment resulted in less severe weight loss, increase in muscle mass and decreased requirement of transfusions. In another placebo-controlled trial of testosterone replacement in men with mild testosterone deficiency following cytotoxic therapy, physical fatigue scores showed significant improvement [34]. All 35 patients in this trial were survivors of hematological malignancies with no evidence of cancer recurrence. The effects of oxandrolone, an oral anabolic steroid, were reported in cancer-related weight loss. Improvements in weight, body cell mass, performance status and quality of life were reported in 37 patients initially. Updated results in 131 patients were reported and confirmed the significant weight gain and body cell mass findings [35]. We believe that these data for non-cancer populations combined with our study findings suggest that low levels of DHEAS and testosterone levels in males have an association with fatigue and provide a reasonable rationale for testing hormone replacement therapy in this select cancer patient population. We have initiated a phase II trial of testosterone supplementation in male cancer patients with low testosterone levels and moderate–severe fatigue. Further study is essential to enhance our understanding of this disabling syndrome and to provide therapeutic relief to our patients.

Acknowledgements

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References


