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Fatigue is associated with inflammation in patients with head and neck cancer before and after intensity-modulated radiation therapy

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ABSTRACT

Patients with head and neck cancer (HNC) receiving intensity-modulated radiation therapy (IMRT) have particularly high rates of fatigue, and pre- and post-radiotherapy fatigue are prognostic factors for pathologic tumor responses and poor survival. Although inflammation has been proposed as one of the potential mechanisms of fatigue in cancer patients, findings have not been consistent, and there is a dearth of longitudinal studies. Accordingly, we conducted a prospective study in 46 HNC patients pre- and one-month post-IMRT. Fatigue was measured by the Multidimensional Fatigue Inventory (MFI)-20 at both time points along with the assessment of peripheral blood inflammatory markers including interleukin (IL)-6, soluble tumor necrosis factor receptor 2, and C-reactive protein (CRP) and gene expression. Generalized estimating equations were used to examine the association between inflammatory markers and fatigue. Gene enrichment analysis using MetaCore software was performed using up-regulated genes that were significantly associated with IMRT and fatigue. Significant associations between fatigue and IL-6 as well as CRP, which were independent of time, were observed. In addition the change in fatigue from pre- to post-IMRT was positively associated with the change in IL-6 and CRP. Analysis of up-regulated gene transcripts as a function of IMRT and fatigue revealed overrepresentation of transcripts related to the defense response and nuclear factor kappa B. In conclusion, our findings support the hypotheses that inflammation is associated with fatigue over time in HNC patients. Future studies on how inflammation contributes to fatigue as well as strategies targeting inflammation to reduce fatigue are warranted.

1. Introduction

Compelling evidence demonstrates the importance of cancer-related fatigue to quality of life and survival (Janaki et al., 2010; Fang et al., 2004; Montazeri, 2009). However, little work has been done in patients with head and neck cancer (HNC) Jereczek-Fossa et al., 2007; Sawada et al., 2012; Ackerstaff et al., 2011; Hoskin et al., 2009. The most prevalent HNCs, cancers of the oral cavity and oropharynx, are the 10th most common cancers worldwide (Mehanna et al., 2010). In the US, 55,070 new HNC cases are estimated in 2014, and this number has increased in the past decade (Siegel et al., 2014). New evidence shows that the rise in incidence of HNCs is due to increased human papillomavirus (HPV) infection. If these trends continue, by 2020 HPV-positive HNCs will likely surpass cervical cancer as the most common HPV-associated cancer in the United States (Chaturvedi et al., 2011). HNC patients, usually treated either definitively or adjuvantly with radiotherapy, have particularly high rates of fatigue (Hickok et al., 2005; Gulliford et al., 2012). Intensity-modulated radiation therapy (IMRT) employs multiple intensity levels across each radiation beam allowing for improved conformal and homogenous dose distributions over complex target volumes with sparing of adjacent normal structures. IMRT is also the most frequently used radiation technique for HNC patients. Recent research on IMRT has shown that patients treated with IMRT experience even higher fatigue compared to conventional, 3D conformal-RT (Gulliford et al.,

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2012; Spratt et al., 2012). IMRT is generally used in combination with concurrent chemotherapy (chemoRT), based on the likely synergistic effect of treatment modalities (Jereczek-Fossa et al., 2007; Bower et al., 2000). Fatigue impacts not only HNC patient's quality of life, but also long term survival Fang et al., 2004; Ackerstaff et al., 2011). It has been estimated that an increase in baseline fatigue of 10 points (out of 100) yields a 17% reduction in survival in this patient population (Fang et al., 2004). Additionally, our previous findings showed that fatigue was significantly correlated with other common and severe treatment-related symptoms such as mucositis, taste change, and dry mouth, all of which form a symptom cluster with fatigue (Xiao et al., 2013, 2014). However, there is no Food and Drug Administration (FDA)-approved pharmacological agent that reliably prevents or treats cancer-related fatigue (Minton et al., 2010).

Understanding the mechanisms of fatigue is critical to its successful management of HNC patients, and may benefit other cancer or treatment-related symptoms as well. Recent research has shown a potential linkage between fatigue and inflammation that may provide novel insights into the biological mechanisms of cancer-related fatigue (Bower et al., 2011; Collado-Hidalgo et al., 2006; Orre et al., 2009; Barsevick et al., 2010). Studies have found that fatigued cancer patients exhibit higher levels of peripheral inflammatory markers, such as interleukin (IL)-1 receptor antagonist (IL-1ra) Collado-Hidalgo et al., 2006; Orre et al., 2009; Bower et al., 2002; Meyers et al., 2005, IL-6 (Meyers et al., 2005; Costanzo et al., 2005; Wratten et al., 2004), tumor necrosis factor (TNF) Bower et al., 2011; Meyers et al., 2005, and C-reactive protein (CRP) Orre et al., 2009, 2011 compared to those without fatigue. Others, however, report no association between fatigue and inflammation (Bower et al., 2011; Cameron et al., 2012). These conflicting findings emphasize the need for further investigation into the relationship between fatigue and inflammation. Additionally, few studies have examined associations between fatigue and inflammation as assessed by gene expression patterns. For instance, one study found that increased expression of transcripts related to nuclear factor kappa B (NFkB), a key mediator for inflammatory responses, in fatigued breast cancer survivors (Bower et al., 2011). However, this study had only 21 patients and utilized a cross-sectional design. Another study in breast cancer patients found that gene expression changes related to NFkB were only apparent in patients receiving chemotherapy, but not increased in those who did not receive chemotherapy (Torres et al., 2013). Although this study also found patients receiving chemotherapy had worse fatigue (Torres et al., 2013), a direct association between gene expression and fatigue was not examined.

To date, no studies have examined the relationship between inflammation and fatigue in HNC patients. Moreover, since most studies in other cancer types have been cross-sectional (Schubert et al., 2007), exploring this association longitudinally may help clarify conflicting findings. The purpose of this study was to examine the longitudinal association between fatigue and inflammation in patients with HNC receiving IMRT. We explored this association at both the protein and gene expression level in peripheral blood and hypothesized that fatigue would be positively associated with increases in protein concentrations of inflammatory markers including CRP, IL-6 and sTNFR2 (as a measure of TNF activity (Fernandez-Real et al., 1998) and gene transcripts related to NFkB signaling pathways.

2. Methods

This prospective, longitudinal study investigated HNC patients 1 week prior to (baseline) and 1 month post completion of IMRT. The overall length of time between the two assessments was approximately 3 months, including 1.5–2 months for IMRT (or chemoIMRT) and 1 month follow-up after the completion of IMRT (or chemoIMRT). Of note, surgery occurred approximately 1 month before IMRT (or chemoIMRT) and therefore before the baseline assessment. After IRB approval, the principal investigator screened participating radiation oncologists' schedules for newly diagnosed patients with HNC. Patients' eligibility was determined by reviewing the electronic medical record. Approximately 80% of screened patients were eligible for this study. Among these patients, 82% were consented to be enrolled into the study. After confirming with the participating radiation oncologist that the patient was eligible and would receive IMRT, the principal investigator or research assistants met with eligible patients to obtain consent before the start of IMRT. All questionnaires were collected at clinic sites, and blood samples were collected by a phlebotomist or certificated nurse on the same day as the questionnaires.

2.1. Sample

The study enrolled patients at the Radiation Oncology Clinics at Emory Clinic and Emory University Hospital Midtown from May, 2012 – December, 2013. Inclusion criteria were: histological proof of squamous cell carcinoma of the head and neck region with no distant metastasis; $\geqslant$21 years of age; and no evidence of uncontrolled metabolic, hematologic, cardiovascular, renal, hepatic or neurologic disease. Exclusion criteria were: simultaneous primaries; previous invasive malignancies but disease free for <3 years; pregnancy; and presence of a major psychiatric disorder (e.g. bipolar disorder and schizophrenia) or inability to understand English. Other exclusion criteria that might confound the relationship between fatigue and inflammation included: chronic medical conditions involving the immune system (e.g., HIV, hepatitis B or C) or regular use of immunosuppressive medications (such as glucocorticoids and methotrexate) within 6 months of study entry. Over-the-counter anti-inflammatory medications and antidepressants were allowed.

2.2. Fatigue and social behavioral measures

2.2.1. Fatigue

The Multidimensional Fatigue Inventory (MFI)-20 was used as the primary outcome measure for fatigue. MFI is a 20-item self-report instrument that covers five dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity (Smets et al., 1995). Each dimension includes four items on a 1- to 5-point scale. The total score, ranging from 20 to 100 (higher scores indicating more fatigue) is calculated as the sum of the five dimensions, and each dimension is the sum of four items. The MFI-20 has well established validity and reliability (α = 0.84) in use with patients with cancer receiving radiation therapy (Schubert et al., 2007; Smets et al., 1995).

2.2.2. Covariates: demographic and clinical variables

Demographic and clinical variables were collected by chart review. Variables included: age, sex, race, education (years), marital status (married/single), body mass index (BMI), antidepressant use (yes/no), tobacco use (yes/no), alcohol use (yes/no), primary cancer site, cancer stage (TNM), radiation dose (Gy), treatment regimen (IMRT/IMRT + chemotherapy/IMRT + chemotherapy + surgery/IMRT + surgery), and chemotherapeutic regimen (cisplatin/carboplatin + paclitaxel/cisplatin switch to carboplatin + paclitaxel). These variables were chosen for their potential influence on fatigue, based on literature reviews and our previous studies (Bower et al., 2011; Wang et al., 2010; Xiao et al., 2011; Mitchell, 2010; Fang et al., 2005).

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