Clinical Predictors of Fatigue in Men With Non-Metastatic Prostate Cancer Receiving External Beam Radiation Therapy

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Background: Fatigue is one of the most distressing symptoms experienced by people with cancer receiving radiation therapy. 

Objectives: The goal of this study is to evaluate clinical predictors of worsening fatigue during external beam radiation therapy (EBRT) in men with non-metastatic prostate cancer.

Methods: Thirty-five men with non-metastatic prostate cancer scheduled for EBRT were followed at baseline, midpoint, and completion of EBRT. The Functional Assessment of Cancer Therapy–Fatigue scale was administered. Demographic and clinical data were obtained by chart review. Paired t-tests, correlations, general linear models, and logistic regressions were used to determine associations between fatigue scores and clinical data.

Findings: Red blood cells, hemoglobin, and hematocrit levels were highly intercorrelated and, therefore, were grouped as one composite variable termed heme. Heme levels at baseline and androgen-deprivation therapy (ADT) were significantly correlated with worsening of fatigue symptoms from baseline to midpoint and endpoint. ADT alone did not have a significant correlation with fatigue, but it indirectly affected fatigue levels by influencing heme markers as treatment progressed. These findings provide evidence that hematologic markers and the use of ADT assist in predicting radiation therapy-related fatigue and guide symptom management.

Cancer-related fatigue (CRF) is defined as a sense of tiredness that persists over time, interferes with activities of daily living, and is not relieved by adequate rest (Hall, Mishel, & Germino, 2014; Piper & Cella, 2010; Weis & Horneber, 2015). Fatigue during external beam radiation therapy (EBRT) has been reported to increase in severity during treatment (Fransson, 2010).

Current guidelines for prostate cancer recommend active surveillance, EBRT, androgen-deprivation therapy (ADT), and/or radical prostatectomy for clinically localized prostate cancer (Brawley, 2012). Although these treatments improve and prolong patients’ lives, side effects often persist long after treatment completion (Singer et al., 2012). Fatigue is among the most distressing symptoms experienced by people with cancer and negatively affects their daily activities, physical well-being and functionality, and relationships with others (Weis & Horneber, 2015). ADT, in particular, may play a role in anemia, which may contribute to fatigue (Guo, Li, & Bhasin, 2014).

The importance of predicting the risk of adverse events associated with cancer treatment cannot be understated; the clinical implications in personalizing cancer therapy and improving nursing care are of great importance. Therefore, the
goal of this study is to evaluate clinical predictors of worsening fatigue in men with non-metastatic prostate cancer using statistical models.

Methods

This study was approved by the Institutional Review Board of the National Institutes of Health (NIH). All patients enrolled in this study were men diagnosed with non-metastatic prostate cancer, with or without prior prostatectomy, and scheduled to receive EBRT with or without concurrent ADT. Patients with progressive diseases causing significant fatigue, psychiatric diseases within the past five years, uncorrected hypothyroidism and anemia, and second malignancies were excluded. Patients who regularly used sedatives (opioids, benzodiazepines, barbiturates) and steroids were excluded because of the drugs’ influence on fatigue. Patients who regularly take nonsteroidal anti-inflammatory agents (NSAIDs) also were excluded from the study because NSAID use is associated with a decline in hemoglobin (Gaskell, Derry, & Moore, 2010). Participants signed written informed consents prior to study participation.

Instruments

Clinical and demographic data were obtained from chart review. To avoid extraneous influences on their responses, participants completed the questionnaires in an outpatient setting before clinical procedures were provided. Questionnaires were completed and blood was drawn for blood cell counts at baseline (D0), midpoint (D21), and completion of EBRT (D42). The 13-item Functional Assessment of Cancer Therapy–Fatigue (FACT-F) scale, a frequently used, validated, reliable, stand-alone measure of CRF (coefficient alpha = 0.95–0.96) was used (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). FACT-F scores ranged from 16–53, with lower scores reflecting higher fatigue intensity. The authors selected one FACT-F item (“I am frustrated by being too tired to do things I want to do.”) as a surrogate in an attempt to quantify mental fatigue. This item was treated separately and was excluded when calculating the total FACT-F scores to avoid spurious correlations. Participants also were screened for depression using the Hamilton Depression Rating Scale (HAM-D) (Lydatt, Denman, McNeilly, Puamula, & Burke, 2008; Milam et al., 2015). HAM-D scores ranged from 16–53, indicating that these patients were able to carry out normal activities. The mean prostate-specific antigen (PSA) level was 5.8 at baseline and virtually 0.00 after completion of EBRT. Mean baseline testosterone, thyroid-stimulating hormone, and albumin levels were all within normal ranges. Depressive symptoms were negligible during and after EBRT with HAM-D scores of all patients falling below 15 and mean scores below 3 (Bech, Paykel, Sireling, & Yiend, 2015).

Statistical Analysis

Descriptive analyses were used to describe demographic characteristics of the sample. Repeated measures analysis of variance (ANOVA) with post hoc paired t-test comparisons were conducted to compare fatigue scores and clinical variables between time points. Correlations between clinical variables and fatigue scores determined interrelationships among these variables during EBRT. Because of substantial variability in fatigue scores, participants were categorized into high change in fatigue (greater than a three-point increase in fatigue scores from D0 to one of the time points during EBRT) and low change in fatigue (D0 to D42) for the logistic regression. The three-point change in fatigue scores has been found to be clinically important in a previous study (Yost, Eton, Garcia, & Cella, 2011). To reduce the number of separate statistical tests, the number of biological/clinical variables was reduced by grouping them into composite measures based on medical rationale. These composite variables were then used in logistic regressions to identify predictors of physical fatigue as well as mental fatigue. Both multiple regression and logistic regression models were used in this study. No replacement value was assigned for missing data. SPSS®, version 19.0, was used to analyze the data. A p value of less than 0.05 indicated statistical significance.

Results

Sample

Clinical characteristics of the patients are summarized in Table 1. The study cohort was comprised of 35 patients with a mean age of 65 years (SD = 7.3), with 27 patients (77%) receiving a total EBRT dose of 75.6 Gray. Most patients had clinical stage T2 prostate cancer and had Gleason scores of either 7 or 8. Twenty-six of the 35 patients enrolled received ADT prior to EBRT, and eight of the patients had undergone radical prostatectomy more than six months prior to EBRT. All but one participant scored 90 on the Karnofsky Performance Scale, indicating that these patients were able to carry out normal activities. The mean prostate-specific antigen (PSA) level was 5.8 at baseline and virtually 0.00 after completion of EBRT. Mean baseline testosterone, thyroid-stimulating hormone, and albumin levels were all within normal ranges. Depressive symptoms were negligible during and after EBRT with HAM-D scores of all patients falling below 15 and mean scores below 3 (Bech, Paykel, Sireling, & Yiend, 2015).

<table>
<thead>
<tr>
<th>Characteristic</th>
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</tr>
<tr>
<td>African American</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
</tr>
<tr>
<td>Total radiation dose (Gray)</td>
<td></td>
</tr>
<tr>
<td>55.8</td>
<td>1</td>
</tr>
<tr>
<td>68.4</td>
<td>7</td>
</tr>
<tr>
<td>75.6</td>
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TABLE 1. Sample Characteristics (N = 35)

<table>
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<tr>
<th>Characteristic</th>
<th>X</th>
<th>Min</th>
<th>Max</th>
<th>SD</th>
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<td>Age (years)</td>
<td>65</td>
<td>53</td>
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<tr>
<td>PSA at baseline</td>
<td>5.8</td>
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<td>PSA after treatment</td>
<td>0.46</td>
<td>0.00</td>
<td>4.84</td>
<td>1.03</td>
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PSA—prostate-specific antigen
Fatigue Scores

Compared to baseline ($\bar{X} = 45, SD = 1.2$), FACT-F scores were lower at midpoint ($\bar{X} = 39.9, SD = 1.7, d = 0.51, p = 0.01$) and completion of EBRT ($\bar{X} = 40.5, SD = 1.5, d = 0.52, p = 0.02$), indicating worsening of fatigue symptoms at these two time points ($F [2, 68] = 8.68, p = 0.0004$) (see Figure 1a). Lower FACT-F scores indicate worsening of fatigue symptoms. Fatigue levels did not change significantly from midpoint to completion of EBRT ($p = 0.81$), indicating that fatigue intensification occurred early in the course of the treatment. The change in mean fatigue scores from baseline to midpoint of EBRT reflects a large effect of EBRT on fatigue symptoms (Cohen’s $d = 0.75$). Similar changes were observed in the one-item mental fatigue surrogate score ($F [2, 68] = 8.48, p = 0.0005$) (see Figure 1b) from baseline ($\bar{X} = 13.7, SD = 0.5$) to midpoint ($\bar{X} = 11.7, SD = 0.7, p = 0.01$) and at completion of EBRT ($\bar{X} = 11.8, SD = 0.7, p = 0.01$).

Two variables were developed based on the fatigue scores. The first variable was fatigue change (FACT-∆), calculated by subtracting fatigue scores at baseline from fatigue scores at EBRT completion. This variable was used to categorize patients into HF (high fatigue change) and LF (low fatigue change) groups. The second variable was mental fatigue (score of 0–4 based on one FACT-F item), which correlated ($r = –0.61, p < 0.01$) with total FACT-F scores at midpoint of EBRT and with fatigue change ($r = 0.75, p < 0.01$). Importantly, the correlation between total FACT-F and mental fatigue scores was significant, although not high enough to suggest that the two variables are equivalent and interchangeable.

Clinical Predictors

The data set used to generate the clinical prediction model included 14 separate biologic variables measured at D0, D21, and D42. Variables were excluded from the model if (a) they did not correlate consistently with other related variables, (b) they did not change during the time points of measurement, and (c) they did change but the changes were not related to fatigue in any way. For example, mean corpuscular volume was not included in the model as the values changed minimally over time. Although absolute lymphocyte count changed substantially from baseline to completion of EBRT, neither its level nor change during EBRT were related to fatigue. Therefore, absolute lymphocyte count was not taken into consideration in the construction of statistical models.

Composite Variables

To develop statistical models based on a relatively small sample size and decrease the likelihood of false correlations, reduction of the number of variables was desirable. This was accomplished by excluding a number of variables from the prediction models and forming composites of correlated variables. Highly correlated variables do not add significant predictive power beyond the other; therefore, it was useful to take colinearity into consideration and form composite variables.

Red blood cells (RBCs), hemoglobin, and hematocrit levels were highly intercorrelated ($r = 0.84–0.95, p < 0.01$) and, therefore, were combined (standardized scores were summed) to form one composite variable, referred to as heme markers. The change in heme levels from baseline to completion of EBRT...
were the two composite variables previously discussed: heme markers and immune cells. A third variable, the use of ADT in adjunction to EBRT, also was included in the prediction model as previous reports suggest ADT affects fatigue during cancer therapy (Kyrdalen, Dahl, Hernes, Hem, & Fossà, 2010; Storey et al., 2012).

As shown in Table 2, the best predictor of fatigue at completion of EBRT was the concomitant use of ADT. Neither of the other two variables (heme markers and immune cells) improved the prediction using the multiple regression model. Heme markers, immune cells, and ADT were entered into the prediction model sequentially using logistic regression. Heme markers proved to be the best predictor of worsening fatigue during EBRT (β = −0.38, p = 0.02). Immune cells, on the other hand, did not have a significant correlation with fatigue (p = 0.41). Of note, although ADT did not have a significant correlation with fatigue (p = 0.1), it indirectly affected fatigue symptoms by influencing heme markers as treatment progressed. Patients who were not on ADT had smaller decreases in heme markers (4.36 compared to 4.01) as well as higher heme values at the completion of EBRT compared to patients on ADT (47.68 to 37.96). Other variables, such as t stage, Gleason score, testosterone level at baseline, PSA level at baseline, and total EBRT dose were excluded from the model because correlations between these variables with fatigue, either singly or in clusters, were not statistically significant (p > 0.15). In addition, when added to the model later, these variables offered no additional predictive value.

Heme markers, immune cells, and ADT were again entered sequentially into the logistic regression model to predict mental fatigue during EBRT. The best predictor of mental fatigue was obtained by entering ADT first (p = 0.02). Adding heme markers improved the prediction, although the coefficient for heme had a p value of only 0.09. As in other models, immune cells added no additional information.

### TABLE 3. Intercorrelation Matrix for Heme Markers, ADT, Total Fatigue, and Mental Fatigue

<table>
<thead>
<tr>
<th>Variable</th>
<th>FACT0</th>
<th>ADT</th>
<th>Heme21</th>
<th>FACT21</th>
<th>Heme42</th>
<th>FACT42</th>
<th>FACT∆</th>
<th>Mental F</th>
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<tbody>
<tr>
<td>Heme0</td>
<td>−0.27</td>
<td>−0.28**</td>
<td>0.68**</td>
<td>0.22</td>
<td>0.57</td>
<td>0.1</td>
<td>−0.45</td>
<td>−0.36</td>
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<tr>
<td>FACT0</td>
<td>-</td>
<td>−0.22**</td>
<td>0.06</td>
<td>0.6</td>
<td>0.12</td>
<td>0.47</td>
<td>−0.05</td>
<td>−0.01</td>
</tr>
<tr>
<td>ADT</td>
<td>-</td>
<td>-</td>
<td>−0.45**</td>
<td>−0.44</td>
<td>−0.44*</td>
<td>−0.49**</td>
<td>0.36*</td>
<td>0.42*</td>
</tr>
<tr>
<td>Heme21</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.28</td>
<td>0.79</td>
<td>0.37</td>
<td>−0.35</td>
<td>−0.2</td>
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<tr>
<td>FACT21</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.29</td>
<td>0.66</td>
<td>0.61</td>
<td>0.67</td>
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<tr>
<td>Heme42</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.33</td>
<td>−0.31</td>
<td>−0.2</td>
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<tr>
<td>FACT42</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<td>0.65</td>
<td>0.56</td>
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<tr>
<td>FACT∆</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01

ADT—andro-gen-deprivation therapy; EBRT—external beam radiation therapy; FACT—Functional Assessment of Cancer Therapy; Mental F—mental fatigue

Note. Heme 0, 21, and 42 indicates heme markers representing red blood cell, hemoglobin, and hematocrit at baseline, day 19–21 or midpoint of EBRT, and day 38–42 or completion of EBRT. FACT0, 21, and 42 indicates scores at baseline, day 19–21 or midpoint of EBRT, and day 38–42 or completion of EBRT. FACT∆ indicates fatigue change or intensification of fatigue from baseline to EBRT completion.
Intercorrelation Matrix of Predictors of Fatigue

Inspection of zero-order correlations showed that FACT-F scores negatively correlated with heme levels (r = –0.35, p = 0.04) and ADT use at baseline (r = –0.22, p = 0.02), suggesting that patients on ADT with low heme levels suffered more severe fatigue symptoms prior to EBRT. This relationship was further observed during EBRT: ADT correlated with low heme levels at D21 (r = –0.37, p = 0.05) and D42 (r = –0.41, p = 0.01), suggesting a suppression effect of ADT on heme levels during EBRT. Although a reduction in heme levels during EBRT is observed in 91% of patients (n = 32), smaller decreases in heme levels were observed in patients who received EBRT with no concomitant ADT.

The relationship between ADT and heme markers during EBRT confirms the negative impact of ADT on fatigue and heme levels during EBRT (D21: r = 0.18, p = 0.03; D42: r = 0.34, p < 0.04). ADT alone worsened fatigue symptoms at midpoint (r = 0.44, p = 0.008), as well as at completion (r = –0.49, p = 0.003) of EBRT. Overall, heme markers at baseline and ADT (r = 0.36, p = 0.03) significantly correlated with changes in FACT-F scores; however, only ADT substantially correlated with one FACT-F item the authors selected as a surrogate marker for mental fatigue (r = 0.42, p = 0.01) (see Table 3). To further confirm the validity of the model, additional regression models were completed with sociodemographic (e.g., race, age) and clinical variables added (e.g., body mass index, baseline levels of albumin and thyroid-stimulating hormone); however, this did not improve the predictability of the model.

A graphical representation of the intercorrelations among heme markers, ADT, and fatigue during EBRT is shown in Figure 2. High levels of heme markers at baseline were associated with high baseline FACT-F (r = –0.27, p = 0.01) as well as high heme levels at midpoint of EBRT (r = 0.68, p < 0.001). Concurrent ADT with EBRT was associated with reduced heme levels at midpoint (r = –0.45, p = 0.006). Heme levels remained highly stable (r = 0.79, p < 0.001) from midpoint to the completion of EBRT, indicating that effects of ADT occur early and are maintained during the course of EBRT. High heme levels at midpoint are associated with low fatigue at midpoint (r = 0.28, p = 0.01). Similarly, heme levels correlated with fatigue severity (r = 0.33, p = 0.04) at completion of EBRT, suggesting that stabilizing heme levels prevents worsening of fatigue symptoms during EBRT. Although no relationship was noted between fatigue scores at baseline and high change in fatigue scores, patients with high levels of heme markers at baseline were more likely to experience worsening of fatigue symptoms during EBRT (r = –0.45, p = 0.006). Mental fatigue worsened during EBRT along with total fatigue, consistent with the high correlation between the two variables both at midpoint (r = 0.67, p < 0.001) and completion (r = 0.56, p < 0.001) of EBRT.

Discussion

Consistent with a previous study that reported that baseline RBC level is the best predictor of fatigue during radiation therapy in women with breast cancer (Witten et al., 2004), the authors found that baseline heme markers predict the trajectory of fatigue during EBRT in men with prostate cancer. This information is uniquely helpful for patients knowing that ADT use in conjunction with EBRT affects heme levels and indirectly influences fatigue. In addition, the study findings can ensure patients that, although their fatigue intensifies at the midpoint of treatment, it does not worsen from midpoint to completion.

Radiation therapy has been shown to induce hematologic toxicities and depress levels of blood cells (Khoshbin et al., 2014; Lee, Mahajan, Das, Sachdeva, & Tiwana, 2015; Pinkawa et al., 2014). Although cancer treatment-induced anemia is a common condition associated with fatigue, the existing literature failed to demonstrate any consistent correlation between fatigue and hemoglobin levels during radiation therapy (Bohlus et al., 2014). Although one study reported no significant difference in hemoglobin and erythropoietin levels between fatigue patients and healthy controls (Winkler et al., 2004), other studies have shown small but significant associations between CRF and anemia (Bohlus et al., 2014; Khoshbin et al., 2014). The current study adds to the existing literature by showing that pre-EBRT hemoglobin levels are the best predictor of fatigue during EBRT in this population.

Androgens have a stimulatory effect on erythropoiesis, and several studies have shown that androgen deprivation either by surgery or through medical castration can lead to a decline in hemoglobin levels (Ahmadi & Daneshmand, 2014; Milam et al., 2015). Previous studies reported that ADT or orchitectomy caused a mild 10% decline in hemoglobin and RBC counts in
men with non-metastatic prostate cancer without anemia prior to receiving the treatment (Grossmann & Zajac, 2012; Moyad & Roach, 2011). The current study confirms the negative impact of ADT on fatigue and heme markers during EBRT.

The authors’ findings show that ADT correlated with a decline in mental fatigue surrogate score. To the best of the authors’ knowledge, this correlation has not been reported previously in this clinical population. One possible explanation of the association may be the ADT-related alteration in the hypothalamic-pituitary-adrenal (HPA) axis. Animal studies have demonstrated associations between altered HPA axis and pro-inflammatory cytokines, which have been shown to result in “sickness behavior,” including fatigue symptoms (Chrousos & Zapantai, 2014; Evers et al., 2014; Fung, Vizcaychipi, Lloyd, Wan, & Ma, 2012; Kasahara & Inoue, 2014).

Limitations

Because of the small sample size and the number of variables used in the prediction model, the number of analyses carried out could have led to some associations being significant by chance. However, patterns of correlations did not appear to be random, which would have been the case if the individual correlations reflected no more than a random process. Another limitation is the use of a single-item surrogate of mental fatigue, which was selected mainly based on the authors’ best judgment. Despite the limitations, the findings in the current study are encouraging, and future studies using a larger sample size and additional time points after radiation therapy are necessary to further validate the prediction model.

Implications for Practice

- Use clinical variables collected prior to treatment to predict worsening fatigue symptoms during cancer treatment.
- Understand the factors that contribute to fatigue during radiation therapy and design optimal treatment strategies.
- Consider the implications of anemia and androgen-deprivation therapy when addressing fatigue symptoms.

Conclusion

Fatigue intensification during EBRT coincided with decreases in heme markers. The influence of clinical variables in fatigue intensification, as described in the statistical model, will assist in fatigue symptom management during radiation therapy. Application of this model to understand factors influencing treatment-related fatigue in other cancer populations would be worthwhile to pursue.

References


