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Serum sTNFR1, IL6, and the Development of Fatigue in Patients with Gastrointestinal Cancer Undergoing Chemoradiation Therapy

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Abstract

Although evidence of inflammation and fatigue has been noted in cancer survivors, whether inflammation is linked to the expression of fatigue and other symptoms arising from concurrent chemoradiation therapy (CXRT) has not been well studied. Patients undergoing CXRT for locally advanced colorectal or esophageal cancer ($n = 103$) reported multiple symptoms weekly via the M. D. Anderson Symptom Inventory (MDASI) from start of therapy. Serum samples were collected weekly to examine changes in inflammatory markers (interleukin [IL]-6, IL-8, IL-10, IL-1 receptor antagonist [IL-1RA], vascular endothelial growth factor [VEGF], and soluble receptor 1 for tumor necrosis factor [sTNF-R1]) via enzyme-linked immunosorbent assay. Relationships between symptom severity and inflammatory-marker concentration levels were estimated using mixed-effect regression analysis, controlled for week of therapy, age, sex, body mass index, pre-CXRT tumor stage, pre-CXRT chemotherapy, pre-CXRT statin use, and type of cancer. Fatigue was the most severe symptom over time, its development profile shared with pain, distress, drowsiness, poor appetite, and disturbed sleep. sTNF-R1 and IL-6 shared a similar pattern of symptom development, with significant increase during CXRT and decrease after completion of CXRT. Serum concentrations of sTNF-R1 were positively associated over time with the severity

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Contributors

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of fatigue ($p = .00097$), while sTNF-R1 and IL-6 were positively related to the severity of a component score of the six most severe symptoms (both $p < .0001$). This longitudinal study suggests a role for over-expressed sTNF-R1 and IL-6 in the development of fatigue and other severe sickness symptoms during CXRT in patients with colorectal or esophageal cancer.

Keywords

fatigue; symptoms; sickness behavior; cytokines; cancer; inflammation; MDASI; chemoradiation

1. Introduction

Concurrent chemoradiation therapy (CXRT) is the treatment of choice for regional, locally advanced colorectal and esophageal cancer, the second most-common stage of these cancers at diagnosis. Both radiation and chemotherapy are aggressive treatments associated with acute treatment-related symptoms that have a deleterious effect on patient functioning and quality of life (Cleeland, 2007). Led by fatigue, a cluster of moderate to severe CXRT-induced symptoms (such as pain, drowsiness, disturbed sleep, poor appetite, and distress) are often simultaneously observed but typically are not closely monitored as toxicities—possibly because, unlike the wide array of resources available for managing pain, few treatments are available for fatigue and other non-specific symptoms. Addressing this issue calls for sophisticated research toward developing a mechanism-driven approach for preventing or treating fatigue and other treatment-related symptoms without compromising tumor control (Cleeland et al., 2003; Wang et al., 2008).

Immune signals from periphery to brain can lead to an exacerbation of sickness behaviors in animal models (Dantzer et al., 2008). Inflammatory cytokines have been reported to associate with typical sickness symptoms in clinical studies, such as depression (Howren et al., 2009), fatigue (Bower et al., 2011a; Collado-Hidalgo et al., 2006; Schubert et al., 2007), and circadian pattern change (Rich et al., 2005), and with radiotherapy-induced symptom burden (Wang et al., 2010) and toxicities such as mucositis (Ong et al., 2010) and lung injury (Hart et al., 2005). Mediating inflammation could thus be a valid intervention target for treatment-induced non-specific symptoms and toxicities in patients with cancer (Cleeland et al., 2003; Lee et al., 2004). However, inflammation management is a new frontier in disease control (Couzin-Frankel, 2010), and there is limited evidence of specific inflammatory marker(s) used as intervention targets.

Translational research on the role of inflammation-related genes and cytokines in fatigue in long-term cancer survivors and terminally ill cancer patients supports a link between inflammation and fatigue, but confirmative results are limited (Bower et al., 2011a; Collado-Hidalgo et al., 2006; Inagaki et al., 2008; Orre et al., 2009; Reinertsen et al., 2011). Tumor necrosis factor (TNF)- α signaling (represented by soluble TNF receptor 2 [sTNF-R2]) was shown to contribute to post-chemotherapy fatigue in early-stage breast cancer patients (Bower et al., 2011b). However, whether inflammation underlies the development of fatigue and sickness symptoms in response to disease and aggressive chemoradiation treatment remains to be established.

Cancer-related fatigue is defined as the patient's perception of unusual tiredness that may result from disease, treatment, or a combination of both (Wang, 2008). In patients with rectal cancer receiving preoperative CXRT, pre-CXRT fatigue scores reported on the M. D. Anderson Symptom Inventory (MDASI) were noted to be independent predictors of treatment outcome (Park et al., 2009), suggesting that baseline fatigue levels may be a surrogate for tumor burden. As a typical patient-reported outcome, fatigue can be measured

effectively with a validated assessment tool (Barsevick et al., 2010). Previous symptom research has established the psychometric validity and clinical utility of the MDASI for simultaneously measuring fatigue and other symptoms in cancer patients undergoing treatment (Cleeland et al., 2000; Wang et al., 2006).

This longitudinal study presents an approach for identifying critical circulating inflammatory markers that associate with the emergence of fatigue as the dose of CXRT accumulates over time. Although fatigue was the primary outcome, we also tracked other symptoms to determine their concordance with fatigue in development pattern and association with specific inflammatory marker(s). Our overall goal was to generate hypotheses for further study of the critical role of inflammation in promoting fatigue and related symptoms. Our working hypothesis for this study was that an over-expressed inflammatory response to CXRT would be temporally associated with a cluster of fatigue-centered, non-specific symptoms (e.g., fatigue, pain, drowsiness, disturbed sleep, lack of appetite, and distress) before, during, and one month after CXRT in patients with colorectal or esophageal cancer.

2. Methods

2.1. Patients and procedures

Patients were recruited consecutively from clinic in the Department of Radiation Oncology, from April 2005 to January 2007, at The University of Texas MD Anderson Cancer Center in Houston, Texas. Eligible patients had a pathological diagnosis of gastrointestinal-tract cancer (which includes cancers of the esophagus, colon, rectum, and anal canal), were scheduled for curative concurrent CXRT, and were at least 18 years old. All eligible patients were enrolled before beginning CXRT, were closely monitored by their treating oncologist, and received standard care for toxicities and complications. The study was approved by the MD Anderson Cancer Center Institutional Review Board. All participants gave written informed consent.

2.1.1. Symptom assessment: M. D. Anderson Symptom Inventory—Patients used the self-administered MDASI to rate the severity of their symptoms before CXRT was begun (baseline) and weekly for 13 weeks from the start of CXRT. The MDASI measures 13 core cancer-related symptoms, including fatigue, during the previous 24 hours on a 0–10 numerical rating scale, with 0 being “not present” and 10 being “as bad as you can imagine” (Cleeland et al., 2000).

2.1.2. Serum inflammatory marker assay—Blood was drawn at baseline, at the patient’s weekly routine clinic visits during the 5–6 weeks of CXRT, and at the 1-month clinic follow-up visit post-CXRT. Ten mL of blood for serum was collected at each time point, usually in the morning or early afternoon (co-incident with the patient’s routine blood tests) and within ± 2 days of MDASI administration. The blood samples were centrifuged to isolate the serum, which was harvested and stored at -20°C for batch analysis.

The serum markers selected for this study included interleukin (IL)-6, IL-8, IL-10, IL-1 receptor antagonist (IL-1RA), vascular endothelial growth factor (VEGF), and soluble receptor 1 for tumor necrosis factor (sTNF-R1). This panel, which included both pro-inflammatory and anti-inflammatory cytokines, was chosen on the basis of results from previous research on symptom expression and inflammation (Dantzer, 2001; Lee et al., 2004; Miller et al., 2008; Wang et al., 2008). We were also interested in whether VEGF (angiogenesis protein) and IL-8 (involved in radiation-induced toxicity) would be released in response to CXRT and could be related to fatigue development. Because of the difficulties inherent in detecting serum TNF- α in similar symptom studies in cancer patients undergoing

CXRT or allogeneic stem cell transplantation (Wang et al., 2008; Wang et al., 2010) and the limited time to process samples described in other human studies (Schubert et al., 2007), TNF- α was not examined. Instead, we examined the serum concentration of sTNF-R1 (which as a TNF- α receptor reflects serum TNF- α activity).

Inflammatory markers were assayed in duplicate using a validated commercial enzyme-linked immunosorbent assay (RayBiotech, Inc, GA), and all values were expressed as the mean of the two measurements. The lower limits of the concentrations were less than 3 pg/mL for IL-6, less than 1 pg/mL for sTNF-R1, IL-8, and IL-10, less than 10 pg/mL for VEGF, and less than 0.1 ng/mL for IL-1RA.

2.1.3. Other patient characteristics—Age, sex, marital status, education level, race, body mass index (BMI), pre-CXRT tumor stage, pre-CXRT hemoglobin and albumin levels, pre-CXRT chemotherapy status, total radiation dose, pre-CXRT statin use, and Eastern Cooperative Oncology Group performance status (ECOG PS) score (Oken et al., 1982) were extracted from medical chart reviews.

2.2. Statistical analysis

Descriptive analysis, including proportions, means, and standard deviations, was used to present patient characteristics. All reported p values are two-tailed and considered significant at $p < 0.05$ for univariate testing. For symptom modeling, multiple comparison adjustment was performed to maintain an overall type I error rate of $p < 0.05$.

Loess curves (Chambers et al., 1983), which are smoothed estimates of average symptom severity as a function of time (during and after CXRT), were constructed for symptom outcomes from all time points.

Means and standard deviations for symptom ratings and absolute values of serum inflammatory markers were computed for three critical time points (pre-CXRT, at the completion of 5–6 weeks of CXRT, and in recovery one month thereafter). A component score was created to represent a fatigue-centered symptom cluster based on the mean of six most severe symptoms from both groups of patients from baseline to 13 weeks.

To explore the relationships between changes in serum concentrations of inflammatory markers and changes in symptom outcomes over time, we analyzed longitudinal fatigue data using ordinal regression modeling and component-score data using generalized linear mixed modeling; for both analyses, serum inflammatory marker levels from all time points were treated as time-dependent covariates, and all symptom data collected for the study was used. Fatigue severity was treated as ordinal responses and protein levels were converted to logarithmic values. Marker data were excluded from the modeling if there was no symptom score for the same time point (± 2 days). Factors that potentially contribute to variation in inflammation expression and symptom development, including age, sex, BMI, pre-CXRT tumor stage, pre-CXRT chemotherapy within one month of enrollment (yes or no), type of cancer (colorectal or esophageal), pre-CXRT statin use (yes or no), and serum level for each marker assayed, were included as covariates in the regression models. A week-of-therapy variable, representing the effect of accumulated dose by time point, was included in the analysis to account for concurrent, systematic trends in symptom reports and marker levels after initiation of CXRT.

3. Results

3.1. Sample characteristics

Table 1 presents the patient and clinical characteristics of the study sample. Patients ($n = 103$) were recruited and contributed longitudinal data; approximately 10% of the eligible patients approached declined to participate. Study enrollment occurred, on average, 76 days from diagnosis. The average total radiation dose administered was 50.4 Gy for esophageal patients and 51.3 Gy for colorectal patients, at 1.8–2.0 Gy per fraction. Radiotherapy was 5 days per week over 5.5 weeks on average. The weekly chemotherapy regimen was capecitabine (orally twice a day on all days of radiation) for most patients with colorectal cancer, and 5-fluorouracil and oxaliplatin (weekly during radiation) for most patients with esophageal cancer. All patients completed the planned treatment regimen for both radiation and chemotherapy. Patients with esophageal cancer were significantly more likely to be men and more likely than colorectal patients to have been treated previously. Most patients had good ECOG PS (0–1) before and after therapy.

3.2. MDASI symptom profiles

All patients contributed symptom data at baseline (week 0) and weekly during CXRT (weeks 1–6) and after CXRT (weeks 7–13). Only three patients were lost to follow-up after completing CXRT. The missing-at-random rate for MDASI symptom data over the 13 weeks was 4%, stemming primarily from administrative error.

Table 2 presents mean values for the most severe patient-reported symptoms pre-CXRT, at the end of CXRT, and one month post-CXRT for each patient sample. For both samples, MDASI fatigue severity ratings increased significantly from pre-CXRT to the end of CXRT ($p < 0.0001$) and decreased significantly from the end of CXRT to one month post-CXRT ($p < 0.0001$); the difference between pre-CXRT and one month post-CXRT fatigue was not statistically significant. Pain was the second most-severe symptom during and after CXRT for patients with colorectal cancer, while difficulty swallowing was the second-worst symptom over time for patients with esophageal cancer.

The Loess curves in Figure 1 show the average symptom severity over the course of CXRT for fatigue and the component score for the fatigue-centered symptom cluster (fatigue, pain, drowsiness, disturbed sleep, lack of appetite, and distress) by each patient sample. Both groups shared the same pattern of symptom development, with peak severity around the end of CXRT. The component score also shared a similar development pattern, although these symptoms were not as severe as fatigue at any time point. At each of these weeks, the component score was significantly different from baseline ratings ($p = 0.005$).

3.3. Serum inflammatory marker profiles

Table 3 presents absolute scores (means and standard deviations) of serum concentrations of all markers at the three time points. Significant differences were observed only for sTNF-R1 ($p = 0.017$) and IL-6 ($p = 0.049$). Sixty-four percent of pre-CXRT data was missing, although most patients contributed samples the first week of CXRT. The missing-at-random rate during CXRT was 12%. Blood draws (656 observations) were completed on the same day as the MDASI assessment 82% of the time; 2% of blood samples did not have a MDASI assessment within ± 2 days and were not included in the modeling.

3.4. Associations between changes in symptom severity and concentrations of inflammatory markers

Women ($p = .006$) and patients with more advanced disease ($p = 0.034$) reported significantly more-severe fatigue over time; see table 4. The component score for fatigue-

centered symptoms was significantly higher for younger patients ($p = 0.009$), women ($p = 0.009$), and patients with advanced cancer (stage III vs. I/II) ($p = 0.045$).

From all 656 pairs of symptom observations and serum marker measurements, ordinal regression models detected a positive associations between sTNF-R1 and fatigue severity ($p = 0.00097$), sTNF-R1 and the component score ($p < 0.0001$), and IL-6 and the component score ($p < 0.0001$) (table 4).

4. Discussion

Fatigue was consistently the most-severe symptom over time for both colorectal and esophageal cancer patients treated with CXRT. Symptom severity consistently peaked around the end of treatment, as did serum sTNF-R1 and IL-6 levels. We identified significant temporal associations between the development of fatigue and increases in serum concentrations of sTNF-R1, and between the severity of a fatigue-centered symptom cluster and increased serum IL-6 and sTNF-R1. These effects could not be accounted for by patient and clinical factors, including age, sex, BMI, type of cancer, staging, or previous chemotherapy or statin use.

Our similar study in patients with non-small cell lung cancer receiving CXRT found that sTNF-R1 was associated with fatigue and other major symptoms (Wang et al., 2010). Another study on radiation alone in breast and prostate cancers found that the downstream markers C-reactive protein and IL-1 receptor antagonist were significantly associated with fatigue (IL-6 and IL-1 β were not) (Bower et al., 2009). Yet another reported that both fatigue and serum IL-1 β tended to rise between weeks 1–4 of radiation for prostate cancer (Greenberg et al., 1993). Although these studies provide no direct evidence of the release of circulating inflammatory markers or angiogenesis with fatigue development, they consistently evidence the temporal association between fatigue and cytokines, receptors, and downstream markers as treatment dose accumulates. These data support our hypothesis that an over-expressed inflammatory response to CXRT may play a critical role in promoting a cluster of fatigue-centered, non-specific symptoms during and after treatment.

As a hypothesis-generating study, our work suggests several possible avenues for future research. First, there is no established animal model of fatigue. This study supports the establishment of an animal model of acute-phase, CXRT-related fatigue to confirm inflammatory mechanisms. A bedside-to-bench approach that utilizes direct evidence from human experience might confirm potential biomarker(s) that are highly relevant to fatigue-centered sickness symptoms.

Second, a causal link between serum inflammatory markers and symptom development cannot be established through discovery studies based on association only; it is possible that inflammation is simply a reflection of other biology that is the primary mechanistic driver of observed symptom and outcome phenomena. Thus, further research is required to explore exactly how inflammation markers may be common denominators mediating the hallmark symptoms of CXRT. Our results support the logical development of clinical trials incorporating concurrent symptom measurement and inflammatory cascade blockade to test pharmacological methods of mitigating symptom burden. In humans, an intervention study using a TNF- α inhibitor was reported to improve tolerability of dose-intensive chemotherapy (Monk et al., 2006).

Finally, the longitudinal design and statistical analysis in this study are essential for modeling and interpreting the role of inflammation in dynamic symptom development. CXRT produces a large insult to the patient within an expected time frame, allowing an investigation of changes. Repeated measures allowed us to identify the emergence of fatigue

and other symptoms, and that symptom severity peaked around the end of CXRT, after dose accumulation has ended, and returned to baseline by one month post-CXRT. This study illustrates how weekly patient-reported symptom data can quantitatively document treatment-related symptom burden over time. Mixed regression modeling is an appropriate approach for the examination of dynamic changes in multiple cytokine and receptor levels and symptom outcomes, and it effectively handles potential confounding factors and random missing data.

Our study had certain limitations. We designed the study to coincide with patients' routine weekly blood-draw schedules, so as to reduce patient burden and the likelihood of missing data. Therefore, the timing of the blood draws may not have been optimal for assaying cytokines with a circadian pattern of release. The relatively high missing-data rate at baseline was resulted from limited feasibility of blood collection at enrollment; however, the blood collection rate one week after baseline provided sufficient marker data. Also, the blood draws may not have occurred on the same day as the scheduled weekly MDASI symptom assessment, although 85% of the time the two measures coincided. We also did not measure nuclear factor-kappa B or glucocorticoid signaling axes as potentially important upstream markers that might contribute to parallel mechanisms of fatigue development. Nevertheless, our results show highly consistent patterns over time in symptom development and change in sTNF-R1 and IL-6, with active control of potential covariates between subjects and with known noise from intraday and interday variability (which might explain the wide range in standard deviations on inflammatory markers in table 4).

In conclusion, the study provided a rationale for further study to confirm the role of sTNF-R1 and IL-6 in the development of chemoradiation-induced, fatigue-centered symptom burden in patients with cancer. These observations argue persuasively for a concerted effort toward reducing the multiple severe symptoms produced by aggressive therapy as an important component of standard care in the oncological management of gastrointestinal cancer, with the ultimate goal of better tolerance of therapy.

Research highlight

Identifying inflammatory markers (here, sTNF-R1 and IL-6) of chemoradiation-induced fatigue is a step toward confirming these biomarkers as a target for mechanism-based symptom management.

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Fig. 1.

Loess curves of the most severe symptoms and markers over time during concurrent chemoradiation: weekly assessment by MDASI.

Loess curves illustrate a gradual increase in symptom severity (on a 0–10 scale) as the dose of concurrent chemoradiation therapy (CXRT) accumulated in patients with gastrointestinal cancer receiving CXRT. MDASI = M. D. Anderson Symptom Inventory; sTNF-R1 = soluble tumor necrosis factor receptor 1; IL-6 = interleukin 6.

Table 1Sample characteristics ($n = 103$)

Demographic characteristics				
		Colorectal cancer ($n = 50$)	Esophageal cancer ($n = 53$)	p
Age, years	Mean (SD)	58.0 (9.9)	60.7 (11.9)	0.22
Sex	Women vs. men	29 vs. 21 (58.0% vs. 42.0%)	9 vs. 44 (17.0% vs. 83.0%)	< 0.001
Marital status	Married	38 (76.0%)	47 (88.7%)	0.09
Education level	More than high school	33 (67.4%)	35 (66.0%)	0.89
Race	White non-Hispanic Black non-Hispanic Hispanic Asian	39 (78.0%) 4 (8.0%) 6 (12.0%) 1 (2.0%)	48 (90.6%) 2 (3.8%) 2 (3.8%) 1 (1.9%)	0.28
Body mass index, kg/m ²	Mean (SD)	29.1 (6.3)	28.6 (5.0)	0.66
Clinical characteristics				
Sample size	Pre-CXRT End of CXRT End of study	50 (100.0%) 50 (100.0%) 49 (98.0%)	53 (100.0%) 53 (100.0%) 52 (98.1%)	
Poor ECOG PS (2–4)	Pre-CXRT End of CXRT	5 (26.3%) 14 (73.7%)	4 (16.7%) 20 (83.3%)	0.48
Previous chemotherapy?	Yes	8 (16.0%)	25 (47.2%)	< 0.001
Pre-CXRT tumor stage	I–II III IV	15 (30.0%) 30 (60.0%) 5 (10.0%)	19 (35.8%) 26 (49.1%) 8 (15.1%)	0.51
Hemoglobin, g/dL, mean (SD)	Pre-CXRT End of CXRT End of study	13.2 (1.4) 12.0 (1.2) 12.7 (1.1)	13.0 (1.8) 12.8 (1.9) 12.7 (1.6)	0.43
Total radiation dose (Gy)	Mean (range)	51.3 (45.0–63.0)	50.4 (45.0–66.0)	0.23
Receiving statin	Yes	14 (28.0%)	20 (37.7%)	0.29

SD = standard deviation; CXRT = concurrent chemoradiation therapy; ECOG PS = Eastern Cooperative Oncology Group performance status.

Table 2

Most severe MDASI symptoms pre-CXRT, at end of CXRT, and one month post-CXRT, mean (SD)

Colorectal Cancer (n = 50)					
Pre-CXRT		End of CXRT		One month post-CXRT	
Fatigue	2.6 (2.8)	Fatigue	4.1 (2.9)	Fatigue	2.1 (2.4)
Distress	2.5 (3.2)	Pain	3.5 (3.3)	Pain	2.0 (3.0)
Disturbed sleep	1.9 (2.7)	Drowsiness	3.2 (2.7)	Disturbed sleep	1.5 (2.0)
Pain	1.7 (2.8)	Soreness at radiation site	3.1 (3.3)	Drowsiness	1.3 (2.3)
Diarrhea	1.7 (2.9)	Lack of appetite	2.8 (3.3)	Distress	1.2 (2.3)
Esophageal cancer (n = 53)					
Pre-CXRT		End of CXRT		One month post-CXRT	
Fatigue	1.7 (2.0)	Fatigue	3.9 (2.7)	Fatigue	2.1 (2.2)
Difficulty Swallowing	1.6 (2.7)	Difficulty Swallowing	3.6 (3.1)	Difficulty Swallowing	1.6 (2.2)
Drowsiness	1.5 (2.3)	Lack of Appetite	3.1 (3.0)	Lack of Appetite	1.6 (2.6)
Distress	1.2 (1.7)	Pain	2.8 (2.7)	Drowsiness	1.4 (1.8)
Disturbed Sleep	1.1 (1.8)	Nausea	2.7 (2.6)	Pain	1.2 (2.1)

MDASI = M. D. Anderson Symptom Inventory; CXRT = concurrent chemoradiation therapy; SD = standard deviation.

Table 3

Serum concentrations (pg/mL) of cytokines in patients with colorectal cancer and esophageal cancer undergoing concurrent chemoradiation therapy; mean (SD)

Colorectal Group						
	<i>n</i>	IL-1RA	IL-6	IL-8	IL-10	sTNF-R1
Pre-CXRT	15	485.1 (1240.0)	17.4 (41.1)	1.2 (1.2)	24.9 (65.9)	152.8 (168.4)
End of CXRT	37	347.2 (1707.5)	23.4 (46.2)	15.1 (56.6)	9.4 (46.7)	114.8 (166.6)
One month post-CXRT	42	298.1 (1641.9)	6.5 (14.1)	23.0 (78.3)	8.5 (44.4)	117.5 (147.4)
Esophageal Group						
	<i>n</i>	IL-1RA	IL-6	IL-8	IL-10	sTNF-R1
Pre-CXRT	20	182.8 (343.8)	6.7 (15.2)	16.1 (41.0)	2.2 (5.3)	93.5 (95.7)
End of CXRT	45	99.8 (165.7)	13.1 (14.1)	12.7 (46.0)	1.5 (2.3)	88.7 (91.2)
One month post-CXRT	48	61.4 (114.9)	8.9 (18.8)	23.6 (132.7)	0.9 (1.9)	105.6 (118.8)

SD = standard deviation; IL = interleukin; IL-1RA = IL-1 receptor antagonist; VEGF = vascular endothelial growth factor; sTNF-R1 = soluble tumor necrosis factor receptor 1; CXRT = concurrent chemoradiation therapy.

Table 4

Mixed effect regression analyses: significance of association between serum cytokines and patient-reported symptom severity over time of CXRT (*p* values)

	Fatigue model	Component score model
Week from start of CXRT	0.7466	0.0050
Age	0.0940	0.0091
Sex (F vs. M)	0.0058	0.0091
BMI	0.6720	0.2650
Stage (III vs. I/II)	0.0342	0.0448
Stage (IV vs. I/II)	0.9420	0.9506
Chemotherapy pre-CXRT within a month (yes vs. no)	0.4450	0.2080
Disease (colorectal cancer vs. esophageal cancer)	0.8881	0.6956
Statin use (yes vs. no)	0.0908	0.0764
Log IL-1RA	0.7086	0.5782
Log IL-6	0.0803	< 0.0001 ^a
Log IL-8	0.2086	0.0643
Log IL-10	0.1781	0.9776
Log VEGF	0.8864	0.5509
Log sTNF-R1	0.00097 ^a	< 0.0001 ^a

CXRT = concurrent chemoradiation therapy; BMI = body mass index; IL = interleukin; IL-1RA = IL-1 receptor antagonist; VEGF = vascular endothelial growth factor; sTNF-R1 = soluble tumor necrosis factor receptor 1.

^aStatistically significant, adjusted for multiple comparisons.