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Inflammatory Cytokines are Associated with the Development of Symptom Burden in Patients with NSCLC Undergoing Concurrent Chemoradiation Therapy

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Abstract

Elevations in cancer treatment-induced circulating inflammatory cytokines may be partially responsible for the development of significant symptom burden (e.g., pain, fatigue, distress, disturbed sleep) during concurrent chemoradiation therapy (CXRT). Sixty-two patients undergoing CXRT for locally advanced non-small cell lung cancer (NSCLC) reported symptoms weekly for 15 weeks via the M. D. Anderson Symptom Inventory (MDASI). Serum inflammatory cytokines were assessed weekly during therapy via enzyme-linked immunosorbent assay. Dynamic changes in cytokines and associated symptom profiles were estimated using mixed-effect models. MDASI symptom severity increased gradually as CXRT dose accumulated and peaked at week 8. Serum concentrations of interleukin (IL)-6, IL-10, and serum soluble receptor 1 for tumor necrosis factor (sTNF-R1) increased significantly by week 8 (all $p < .05$). During CXRT, controlled for age, sex, race, body mass index, cancer recurrence, previous treatment status, total radiotherapy dose, and CXRT delivery technique, an increase in sTNF-R1 was significantly related to an increase in the mean score for all 15 MDASI symptoms (estimate, 1.74; SE, 0.69; $p < .05$) and to a larger radiation dose to normal lung volume (estimate, 1.77; SE, 0.71; $p < .01$); an increase in serum IL-6 was significantly related to increased mean severity for the five most severe symptoms (pain, fatigue, disturbed sleep, lack of appetite, sore throat) (estimate, 0.32; SE, 0.16; $p < .05$). These results suggest a role for over-expressed pro-inflammatory cytokines in significant worsening of symptoms in NSCLC patients undergoing

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CXRT, and warrant further study to identify biological targets for ameliorating treatment-related symptom burden.

Keywords

Symptom; inflammatory cytokines; MDASI; NSCLC; chemoradiation; mixed-effect model

1 Introduction

Lung cancer is a highly symptomatic disease that has the second-highest yearly incidence rate among all cancers in the United States (Jemal et al., 2009). Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer. The treatment of choice for loco-regional and advanced NSCLC is concurrent chemoradiation therapy (CXRT) (Jemal et al., 2009; Yamamoto et al., 2006), a modality that is frequently associated with multiple symptoms induced by accumulating doses of radiation and chemotherapy (Wang et al., 2006).

However, with the exception of pain, many non-specific cancer symptoms—such as fatigue, disturbed sleep, poor appetite, and distress—are not intentionally monitored in the clinical setting and may not be treated as specific toxicities of cancer or cancer treatment (Cleeland, 2000; Cox et al., 1995; Patrick et al., 2004). Collectively, these non-specific symptoms and toxicities form a “symptom burden” that can affect patient functioning. Symptom burden may provoke treatment interruptions, such as dose reduction or withdrawal from chemotherapy and/or radiotherapy for patients with NSCLC, which could compromise the effectiveness of intervention (Cleeland, 2007).

Controlling symptoms requires first that they be assessed, preferably throughout the course of treatment. The subjective nature of the symptom experience has necessitated the use of validated multiple-symptom assessment instruments that can capture the patient's own report of the severity of symptoms (so-called patient-reported outcomes).

Controlling symptoms also requires a better understanding of the mechanism(s) underlying the development of treatment-related symptoms. Recent cancer research has shown that symptoms such as pain, fatigue, and disturbed sleep frequently cluster together and often share the same developmental pattern over the trajectory of disease progression and treatment (Barsevick et al., 2006; Cleeland et al., 2003; Dodd et al., 2001; Fan et al., 2007; Hickok et al., 2005; Wang et al., 2006). This symptom clustering suggests that common biological mechanisms may underlie the development of multiple cancer treatment-related symptoms. Dysregulation of inflammatory cytokines has been suggested as one possible common biological mechanism of multiple-symptom production (Cleeland et al., 2003; Dantzer, 2001; Lee et al., 2004; Miller et al., 2008; Rube et al., 2004; Wang et al., 2008). The over-response of inflammatory cytokines to the insult from aggressive cancer therapy has been studied in radiation pneumonitis and other clinical outcomes, but the possibility that CXRT-induced fluctuations in circulating cytokines may trigger the development of symptoms has only recently been studied in limited cohorts of cancer patients (Bower et al., 2002; Bower et al., 2009; Hart et al., 2005; Meyers et al., 2005; Miller et al., 2008; Wratten et al., 2004).

Investigating the possible role of inflammatory cytokines in producing symptom burden in patients being treated with chemoradiotherapy for NSCLC requires identification of specific cytokines and evidence of their correlation with the emergence of the most severe symptoms during CXRT. We therefore designed a longitudinal descriptive study with patient-reported symptoms as primary outcomes; symptoms were assessed via the M. D. Anderson Symptom Inventory (Cleeland et al., 2000). Our goals were (1) to establish patterns of dynamic changes

in both symptoms and serum levels of inflammatory cytokines by examining the effect of CXRT on their development, and (2) to track and identify the critical interaction between serum concentrations of inflammatory cytokines and the development of multiple symptoms in patients with NSCLC undergoing CXRT. We hypothesized that the cumulative dose of CXRT in patients with NSCLC would induce an over-expression of certain inflammatory cytokines during therapy, promoting the development of multiple symptoms that would worsen over time.

2 Methods

2.1 Patients

Patients with NSCLC were recruited consecutively from clinic in the Department of Radiation Oncology at The University of Texas M. D. Anderson Cancer Center in Houston, Texas. Eligible patients were scheduled for curative CXRT, were at least 18 years old, and had a pathological diagnosis of unresectable NSCLC. The study was approved by the M. D. Anderson Cancer Center Institutional Review Board. All participants gave written informed consent.

2.2 Assessments

2.2.1 The M. D. Anderson Symptom Inventory—Patient-reported outcomes for symptom severity were collected weekly for 15 weeks from before CXRT via the self-administered M. D. Anderson Symptom Inventory (MDASI) (Cleeland et al., 2000). The MDASI is a valid, straightforward, easily understood assessment instrument that is sensitive to symptom changes caused by changes in disease status or treatment over time (Kirkova et al., 2006). The MDASI includes 13 core symptom items (fatigue, disturbed sleep, pain, drowsiness, poor appetite, nausea, vomiting, shortness of breath, numbness, difficulty remembering, dry mouth, distress, sadness). For this study, we also assessed two additional symptoms (coughing and sore throat) that are specific to lung cancer and radiotherapy (Wang et al., 2006). The severity of each symptom during the previous 24 hours is assessed on a 0–10 numerical rating scale, with 0 being “not present” and 10 being “as bad as you can imagine.”

Four MDASI component scores were used as outcomes to represent various aspects of symptom burden: (1) the mean of the five most severe symptoms at the end of CXRT, representing the most burdensome physical symptoms in this cohort of patients; (2) the mean of all 15 MDASI symptom items, representing overall symptom burden; (3) the mean of the two esophagitis-related symptoms (pain, sore throat), representing toxicity induced specifically by therapy (Wang et al., 2006); and (4) the mean of the two affective symptoms (distress, sadness), representing psychological symptoms that might be related to different cytokines than are physical symptoms.

2.2.2 Serum inflammatory cytokine assay—Blood samples were obtained from each patient at baseline (prior to the start of CXRT) and weekly thereafter during approximately eight weeks of therapy (usually in the morning or early afternoon, co-incident with the patient's routine weekly blood tests, and usually on the day of MDASI administration $\pm$ 1–2 days). After the blood draw, samples were put on ice until they could be delivered to the research refrigerator for storage while awaiting processing. Blood samples were delivered to the research laboratory within 2–4 hours on average, although a few samples were not delivered for approximately 24 hours. Blood samples were centrifuged to isolate the serum, which was then harvested and stored at -20°C for batch analysis. The serum cytokines selected for this study included interleukin (IL)-6, IL-8, IL-10, IL-12p40p70, IL-1 receptor antagonist (IL-1RA), tumor necrosis factor (TNF)- α , and soluble receptor 1 for TNF (sTNF-R1). This cytokine panel was chosen on the basis of results from previous research on symptom expression and inflammation (Cleeland et al., 2003; Dantzer, 2001; Lee et al., 2004; Miller et al., 2008; Wang et al., 2008).

Cytokine concentrations were assayed individually 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 detectable concentrations were 3 pg/mL for IL-6, 15 pg/mL for TNF- α , and 1 pg/mL for sTNF-R1, IL-8, IL-10, and IL-12p40p70.

2.2.3 Other patient and clinical characteristics—Factors to be controlled in modeling the symptom and cytokine fluctuations were extracted from medical chart reviews. Demographic variables included age, sex, race, and body mass index (BMI); clinical variables included baseline Eastern Cooperative Oncology Group performance status (ECOG PS) score, recurrence of cancer (Y/N), previous chemotherapy (Y/N), and radiation dose. Radiotherapy technique was either 3-dimensional conformational radiation therapy (3D-CRT) or the more tissue-sparing intensity-modulated radiation therapy (IMRT). The volume of normal lung receiving at least 20 Gy (V20) is a significant radiation dosimetric variable that predicts radiation-related toxicity in patients with NSCLC (Barcellos-Hoff, 1998; Graham et al., 1999; Liao et al., 2009). Radiation dose volume histogram (DVH) represents the delivered doses and volume of target structures irradiated during treatment.

2.3 Statistical analysis

Descriptive analysis was used to examine patient characteristics. Lowess curves present a smoothed average level of symptom severity as a function of time (which in this study indicated the accumulating therapeutic dose of chemoradiation) measured in weeks. Lowess curves were constructed for the 15-week symptom assessment period beginning at baseline for each of the four component scores of symptom burden.

Mixed-effect modeling was used (1) to examine weekly changes in the severity of the component score for all 15 MDASI symptom items, compared with baseline as the control; (2) to examine weekly changes relative to baseline in serum cytokine concentrations during CXRT; (3) to identify cytokines significantly associated with symptom increase during the eight weeks of CXRT that cytokine data were collected; and (4) to explore whether V20 was related to changes in both serum cytokine levels and symptom severities, using serum cytokine levels as time-dependent variables and symptom component (mean) scores to represent symptom severity (Fairclough and Wang, 2005). To address skewed distributions of cytokine values, we used log-transformed cytokines in the mixed models. All mixed models were produced using SAS PROC MIXED statistical package (SAS v9.2; Littell et al., 1996) with spatial power law [SP(POW)] covariance structure for unequally spaced data and adjustment of time-independent variables. The best-fitting models were selected on the basis of Bayesian information criterion (BIC; SAS analysis). Statistical significance was defined as $p < .05$; all tests were two-tailed.

3 Results

3.1 Patient sample

Sixty-two patients were recruited for the study and all patients completed the treatment regimen. Approximately 10% of the eligible patients approached declined to participate. Patients were administered a total radiation dose of 50–70 Gy (mean 64 Gy, SD 7) over an average of 6.5 weeks, at 1.8–2.0 Gy per fraction daily. A standard platinum-taxane-based chemotherapy regimen was concurrently administered to all patients during radiotherapy. All patients had good performance status (ECOG PS = 0–1) before therapy. See Table 1 for patient demographics and cancer staging and therapy information.

3.2 Symptom profiles

All patients contributed symptom data at baseline and during CXRT. Two patients died of pneumonia within two weeks of completing CXRT. For longitudinal symptom data, the random missing-data rate was 8.5%, stemming primarily from patient fatigue or administrative error.

Symptom severity, represented by MDASI component symptom scores based on the MDASI's 0–10 scale, gradually increased from baseline during CXRT. Dynamic changes in symptoms over time were examined by mixed-model estimates of the weekly changes in the 15-symptom component score relative to baseline (the control value) (Table 2). Positive estimate values indicated that the weekly component symptom scores for 15 symptoms during weeks 4–12 were higher than baseline (all $p < .05$ for weeks 4–5 and weeks 11–12; all $p < .0001$ for weeks 6–10). Overall symptom severity peaked at week 8 of CXRT and did not approach its baseline level until week 13, about 6 weeks post-therapy. On average, from week 0 to week 8, the symptom component score increased 0.16 points on the MDASI's 0 to 10 scale each week; from week 8 to week 15, the component score decreased 0.16 points each week. These significant weekly changes in symptom severity could not be accounted for by age, sex, race, BMI, recurrence of cancer, dose of radiation, previous chemotherapy, or type of radiotherapy.

The Lowess curves in Fig. 1 show the average component scores for symptom severity during and after CXRT for the four symptom outcomes. At week 7, the average component score for the physical symptoms was significantly higher than the average component score for the two affective symptoms (3.99 ± 2.34 vs. 2.02 ± 2.69 , $p < .0001$). There was no significant change over time of CXRT in the component score for affective symptoms, whereas the other three component scores fluctuated significantly (Table 3).

3.3 Cytokine profiles

Using 8 weeks of serum cytokine data, mixed modeling detected a significant weekly increase in IL-6 (est, 0.044, SE, 0.017, $p = .0132$), which means that, on average, IL-6 increased 4.4% each week. There were also significant weekly increases in sTNF-R1 (est, 0.007, SE, 0.004; $p = .027$) and IL-10 (est, 0.018, SE, 0.006, $p = .005$). No significant changes were observed during CXRT for IL-1RA, IL-8, or IL-12p40p70. Serum TNF- α was not detectable in any of the samples and therefore was not included in final analysis. These weekly increases in concentration could not be accounted for by age, sex, race, BMI, dose of radiation, recurrence of disease, type of radiation, or previous chemotherapy status. Fig. 2 presents weekly serum concentrations for IL-6, sTNF-R1 and IL-10, the three cytokines increased significantly during CXRT.

3.4 Associations among inflammatory cytokines, multiple symptoms, and radiation

With 266 observations from baseline through eight weeks of therapy (the period for which we had both symptom and cytokine data), and controlled for age, sex, race, BMI, recurrence of cancer, previous chemotherapy status, total radiotherapy dose, and type of radiotherapy technique (IMRT vs 3D-CRT), we observed significant associations between changes in serum cytokines and various symptom outcomes (Table 3).

IL-6 was the only cytokine whose increase was associated with increase in the mean severity of the five most severe symptoms (pain, fatigue, disturbed sleep, lack of appetite, sore throat) (est, 0.32; SE, 0.16; $p < .05$). The estimate parameter in Table 3 indicates that a double increase in IL-6 concentration was associated with an average increase of 0.22 in the mean of the five most severe symptoms on a 0–10 scale on any week during CXRT.

During CXRT, serum sTNF-R1 was the only cytokine whose increase was significantly associated with an increase in the 15-symptom component score (est, 1.74; SE, 0.69; $p < .05$)

(Table 3). Increased serum IL-6 (est, 0.77; SE, 0.19; $p < .0001$) and decreased IL-8 (est, -0.49 ; SE, 0.17; $p < .01$) were significantly associated with increased esophagitis-related symptoms (pain and sore throat) that were likely induced by radiation.

In a subgroup of the sample ($n = 38$) for whom V20 and DVH data was available, the mixed models showed that during CXRT, the volume of normal lung receiving at least 20 Gy of radiation (V20) was significantly associated with both increased serum sTNF-R1 (est, 1.77; SE, 0.71; $p < .01$) and increased total symptom burden (moderate to severe levels; est, 23.88; SE, 11.29; $p < .05$). No significant associations were found between DVH and either symptoms or cytokines.

4 Discussion

This longitudinal study demonstrated, in response to accumulating combined radiation and chemotherapy in patients with NSCLC, (1) a significant worsening of symptom burden during CXRT that peaked at week 8; (2) a significant increase in serum IL-6, sTNF-R1, and IL-10 during 8 weeks of CXRT, perhaps as a result of tissue destruction; and (3) association between over-expressed serum concentrations pro-inflammatory cytokines (primarily sTNF-R1 and IL-6) and worsening treatment-related symptoms.

CXRT with systemic chemotherapy and a sufficient dose and volume of radiotherapy can control tumor recurrence and the spread to nearby lymph nodes in locally advanced NSCLC. Although many therapeutic strategies to relieve the acute complications of CXRT have been integrated into patient care (eg, anti-inflammatory agents, analgesics, hydration, nutrition) (Bradley et al., 2004), we observed increase in both non-specific symptoms and treatment-related toxicities (Hickok et al., 2005) during therapy for this cohort of patients with NSCLC. This was especially true for the most severe physical symptoms (pain, fatigue, lack of appetite, disturbed sleep, sore throat). The component score for total symptom burden (all 15 MDASI symptoms) increased gradually during CXRT, reached significant difference from baseline at week 4, peaked in severity after completion of therapy at week 8, and remained high for several more weeks, not returning to baseline severity until week 13. The results showing that symptoms peaked after treatment had ended could help to establish expectations of post-treatment symptom burden and highlight the need for more effective post-treatment symptom control.

Patients entering the study may already have been experiencing NSCLC-related symptoms; therefore, using their baseline symptom and cytokine assessments as the control for the study was an appropriate way to measure the effect of time (measured in weeks), and therefore the effect of accumulating chemoradiation dose, on the dynamic changes in patients' CXRT-related symptom profiles. The results of this study add to the knowledge of aggressive therapy-induced dynamic changes in the quantitative relationship between symptom severity and inflammatory cytokines. Tests of the hypothesis that sickness behavior is induced by cytokine dysregulation have shown evidence of IL-6, IL-1RA, IL-1, TNF- α (Rube et al., 2002), albumin (Meyers et al., 2005; Schubert et al., 2007), and neopterin (Bower et al., 2002) in patients and survivors with cancer-related fatigue and in depressed patients (Miller et al., 2008). The use of a TNF- α inhibitor has been reported to improve tolerability of dose-intensive chemotherapy in patients with cancer (Graham et al., 1999).

Serum TNF- α was undetectable in this patient cohort. However, the serum concentrations of sTNF-R1 (which as a TNF- α receptor reflects serum TNF- α activity) were normally distributed and sufficiently robust to detect a significant week-by-week change, as shown in Fig. 2. There are several possible reasons that TNF- α was not detectable. First, TNF- α levels may have been affected by the prolonged hours associated with the sampling process in human cytokine studies

(Schubert et al., 2007), as TNF- α is known to be highly sensitive to sampling conditions (Thavasu et al., 1992). Second, it is possible that the concentration of measurable free TNF- α in this cohort of patients actually was very low.

IL-6 was significantly associated with the most severe physical symptoms, but not all 15 symptoms, in this cohort of patients. This is consistent with another symptom study showing that serum IL-6 was highly correlated with a rapid increase in severe physical symptoms at white blood count nadir among cancer patients undergoing allogeneic stem cell transplantation (Wang et al., 2008). Together, these studies further confirm the preliminary impression of the significant positive effect of IL-6 on cancer-related fatigue discussed in the quantitative review by Schubert and colleagues (Schubert et al., 2007).

Disease-driven cytokine dysregulation has been recognized (Germano et al., 2008), and reported as prognostic biomarker for poor clinical outcomes in cancer. In our study, baseline (pre-CXRT) serum concentrations of both IL-6 and sTNF-R1 were already higher than previously reported normal concentrations (Miles et al., 1992; Preti et al., 1997; Trikha et al., 2003). Accordingly, the over-expression of serum cytokines during CXRT appears to have been induced by both cancer and aggressive cancer therapy. The cytokines selected for this study were common pro-inflammatory and anti-inflammatory cytokines that have been reported in animal sickness behaviors, such as IL-6, IL-1RA, TNF- α , and sTNF-R1. We also included IL-8, IL-10, and IL-12p40p70 because they have been investigated for predicting the effect and acute complications of radiation therapy in humans.

The therapeutic radiation dose to tumor was a relatively fixed factor in this study. However, the volume of tissue (including normal lung tissue) irradiated by at least 20 Gy (V20) varied by individual patient. A larger V20 score was associated with increased serum levels of sTNF-R1, and both a larger V20 score and an increased serum level of sTNF-R1 were associated with an increased risk for moderate to severe overall symptoms in these NSCLC patients undergoing CXRT.

The homogeneous sample, validated patient-reported outcome measure (MDASI), longitudinal design with both symptom and cytokine data collection, and mixed-effects statistical analysis in this study were essential for modeling and interpreting the role of cytokines in dynamic symptom development due to CXRT. Given the complexity of the role of inflammatory cytokines in both disease and symptom outcomes in cancer patients, we believe that mixed modeling, a statistical method that provides standardized coefficients (estimate scores), is an appropriate approach for the examination of dynamic changes in multiple cytokine levels and symptom outcomes. This method effectively handles missing data and controls for potential confounding (Fairclough and Wang, 2005).

Our study had certain limitations. We designed our study to coincide with patients' routine 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 and could have missed peak levels of cytokines with a circadian pattern of release, such as IL-6 and TNF- α . Also, the blood draws may not have occurred on the same day as the scheduled weekly symptom assessment, and a few samples, although kept on ice, were delayed up to 24 hours before being delivered to the research lab for processing; either of these situations could have introduced noise into the data. Further, because it was not feasible to require patients to return to the clinic for a research blood draw upon completion of therapy, we did not collect serum samples for cytokine analysis during the CXRT recovery phase. With 15 weeks of symptom data but only eight weeks of serum samples per patient, we could not establish whether serum levels of inflammatory cytokines declined after cessation of therapy (as did symptom severity) or model the association between multiple symptom burden and cytokine levels for the post-treatment

period. Finally, we used sTNF-R1 as a substitute marker for TNF- α , which was our original target but was not detectable in our study. It is possible that a high-sensitivity TNF- α assay could have detected this cytokine without our having to resort to a substitute. Nonetheless, we are satisfied that measuring sTNF-R1 was an appropriate method for assessing the significant effect of tumor necrosis factor.

In conclusion, the current study provides evidence that over-expressed sTNF-R1 is positively associated with the amount of lung tissue irradiated (indicated by V20) and with a rapid increase in overall symptom burden, and that over-expressed IL-6 is associated with increase in the most severe physical symptoms in response to accumulated radiation plus chemotherapy, an aggressive cancer treatment for NSCLC. This inflammatory response may underlie the development of multiple co-occurring CXRT-induced sickness symptoms and, if so, it could provide a target for effective symptom management that focuses on the inflammation pathway to help patients with NSCLC better tolerate their curative therapy.

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References

- Barcellos-Hoff MH. How do tissues respond to damage at the cellular level? The role of cytokines in irradiated tissues. *Radiat. Res* 1998;150:S109–S120. [PubMed: 9806614]
- Barsevick AM, Whitmer K, Nail LM, Beck SL, Dudley WN. Symptom cluster research: conceptual, design, measurement, and analysis issues. *J Pain Symptom Manage* 2006;31:85–95. [PubMed: 16442485]
- Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom. Med* 2002;64:604–611. [PubMed: 12140350]
- Bower JE, Ganz PA, Tao ML, Hu W, Belin TR, Sepah S, Cole S, Aziz N. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clin Cancer Res* 2009;15:5534–5540. [PubMed: 19706826]
- Bradley J, Deasy JO, Bentzen S, El-Naqa I. Dosimetric correlates for acute esophagitis in patients treated with radiotherapy for lung carcinoma. *Int. J. Radiat. Oncol. Biol. Phys* 2004;58:1106–1113. [PubMed: 15001251]
- Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. *J Natl Cancer Inst Monogr* 2007;37:16–21. [PubMed: 17951226]
- Cleeland CS. Cancer-related symptoms. *Semin. Radiat. Oncol* 2000;10:175–190. [PubMed: 11034629]
- Cleeland CS, Bennett GJ, Dantzer R, Dougherty PM, Dunn AJ, Meyers CA, Miller AH, Payne R, Reuben JM, Wang XS, Lee BN. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? *Cancer* 2003;97:2919–2925. [PubMed: 12767108]
- Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, Engstrom MC. Assessing symptom distress in cancer patients: the M. D. Anderson Symptom Inventory. *Cancer* 2000;89:1634–1646. [PubMed: 11013380]
- Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int. J. Radiat. Oncol. Biol. Phys* 1995;31:1341–1346. [PubMed: 7713792]
- Dantzer R. Cytokine-induced sickness behavior: where do we stand? *Brain. Behav. Immun* 2001;15:7–24. [PubMed: 11259077]
- Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. *Oncol. Nurs. Forum* 2001;28:465–470. [PubMed: 11338755]

- Fairclough, DL.; Wang, XS. Understanding the correlations between biologic and symptom measures over time.. In: Lenderking, WR.; Revicki, DA., editors. *Advancing Health Outcomes Research Methods and Clinical Applications*. Degnon Associates; McLean, VA: 2005. p. 177-190.
- Fan G, Filipczak L, Chow E. Symptom clusters in cancer patients: a review of the literature. *Curr. Oncol* 2007;14:173–179. [PubMed: 17938700]
- Germano G, Allavena P, Mantovani A. Cytokines as a key component of cancer-related inflammation. *Cytokine* 2008;43:374–379. [PubMed: 18701317]
- Graham MV, Purdy JA, Emami B, Harms W, Bosch W, Lockett MA, Perez CA. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int. J. Radiat. Oncol. Biol. Phys* 1999;45:323–329. [PubMed: 10487552]
- Hart JP, Broadwater G, Rabbani Z, Moeller BJ, Clough R, Huang D, Sempowski GA, Dewhirst M, Pizzo SV, Vujaskovic Z, Anscher MS. Cytokine profiling for prediction of symptomatic radiation-induced lung injury. *Int J Radiat. Oncol Biol Phys* 2005;63:1448–1454. [PubMed: 16115739]
- Hickok JT, Morrow GR, Roscoe JA, Mustian K, Okunieff P. Occurrence, severity, and longitudinal course of twelve common symptoms in 1129 consecutive patients during radiotherapy for cancer. *J Pain Symptom Manage* 2005;30:433–442. [PubMed: 16310617]
- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA. Cancer. J. Clin* 2009;59:225–249.
- Kirkova J, Davis MP, Walsh D, Tiernan E, O'Leary N, LeGrand SB, Lagman RL, Russell KM. Cancer symptom assessment instruments: a systematic review. *J Clin Oncol* 2006;24:1459–1473. [PubMed: 16549841]
- Lee BN, Dantzer R, Langley KE, Bennett GJ, Dougherty PM, Dunn AJ, Meyers CA, Miller AH, Payne R, Reuben JM, Wang XS, Cleeland CS. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. *Neuroimmunomodulation* 2004;11:279–292. [PubMed: 15316238]
- Liao ZX, Komaki RR, Thames HD Jr, Liu HH, Tucker SL, Mohan R, Martel MK, Wei X, Yang K, Kim ES, Blumenschein G, Hong WK, Cox JD. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2009
- Littell, RC.; Milliken, GA.; Stroup, WW.; Wolfinger, RD. Analysis of repeated measures data.. In: Littell, RC.; Milliken, GA.; Stroup, WW.; Wolfinger, RD., editors. *SAS System for Mixed Models*. SAS Institute, Inc; Cary NC: 1996. p. 87-134.
- Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. *Cancer* 2005;104:788–793. [PubMed: 15973668]
- Miles DW, Aderka D, Engelmann H, Wallach D, Balkwill FR. Induction of soluble tumour necrosis factor receptors during treatment with interleukin-2. *Br J Cancer* 1992;66:1195–1199. [PubMed: 1333789]
- Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol* 2008;26:971–982. [PubMed: 18281672]
- Patrick, DL.; Ferketich, SL.; Frame, PS.; Harris, JJ.; Hendricks, CB.; Levin, B.; Link, MP.; Lustig, C.; McLaughlin, J.; Reid, LD.; Turrisi, AT., III; Unutzer, J.; Vernon, SW. National Institutes of Health State-of-the-Science Conference Statement: Symptom management in cancer: pain, depression, and fatigue; *J. Natl. Cancer Inst. Monogr.* July 15-17, 2002; 2004. p. 9-16.
- Preti HA, Cabanillas F, Talpaz M, Tucker SL, Seymour JF, Kurzrock R. Prognostic value of serum interleukin-6 in diffuse large-cell lymphoma. *Ann Intern Med* 1997;127:186–194. [PubMed: 9245223]
- Rube CE, Wilfert F, Uthe D, Konig J, Liu L, Schuck A, Willich N, Remberger K, Rube C. Increased expression of pro-inflammatory cytokines as a cause of lung toxicity after combined treatment with gemcitabine and thoracic irradiation. *Radiother. Oncol* 2004;72:231–241. [PubMed: 15297141]
- Rube CE, Wilfert F, Uthe D, Schmid KW, Knoop R, Willich N, Schuck A, Rube C. Modulation of radiation-induced tumour necrosis factor alpha (TNF-alpha) expression in the lung tissue by pentoxifylline. *Radiother. Oncol* 2002;64:177–187. [PubMed: 12242128]

- Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun* 2007;21:413–427. [PubMed: 17178209]
- Thavasu PW, Longhurst S, Joel SP, Slevin ML, Balkwill FR. Measuring cytokine levels in blood. Importance of anticoagulants, processing, and storage conditions. *J Immunol Methods* 1992;153:115–124. [PubMed: 1381403]
- Trikha M, Corringham R, Klein B, Rossi JF. Targeted anti-interleukin-6 monoclonal antibody therapy for cancer: a review of the rationale and clinical evidence. *Clin Cancer Res* 2003;9:4653–4665. [PubMed: 14581334]
- Wang XS, Fairclough DL, Liao Z, Komaki R, Chang JY, Mobley GM, Cleeland CS. Longitudinal study of the relationship between chemoradiation therapy for non-small-cell lung cancer and patient symptoms. *J Clin Oncol* 2006;24:4485–4491. [PubMed: 16983118]
- Wang XS, Shi Q, Williams LA, Cleeland CS, Mobley GM, Reuben JM, Lee BN, Giralt SA. Serum interleukin-6 predicts the development of multiple symptoms at nadir of allogeneic hematopoietic stem cell transplantation. *Cancer* 2008;113:2102–2109. [PubMed: 18792065]
- Wratten C, Kilmurray J, Nash S, Seldon M, Hamilton CS, O'Brien PC, Denham JW. Fatigue during breast radiotherapy and its relationship to biological factors. *Int J Radiat. Oncol Biol Phys* 2004;59:160–167. [PubMed: 15093912]
- Yamamoto N, Nishimura Y, Nakagawa K, Matsui K, Fukuoka M. Phase I/II study of weekly docetaxel dose escalation in combination with fixed weekly cisplatin and concurrent thoracic radiotherapy in locally advanced non-small cell lung cancer. *Cancer. Chemother. Pharmacol* 2006;58:285–291. [PubMed: 16416334]

Fig. 1.

Lowess curves of symptom profiles: Average severity levels of component scores in patients with non-small cell lung cancer receiving concurrent chemotherapy treatment (CXRT).

* Five most severe symptoms: pain, fatigue, lack of appetite, disturbed sleep, and sore throat.

Fig. 2.

Serum IL-6 and sTNF-R1 concentrations during concurrent chemoradiation therapy in patients with NSCLC. The rectangular box represents the interquartile range of the observed distribution of values. Horizontal lines within boxes represent the median. Whiskers span minimum to maximum observed values, with algorithm-defined outliers identified by open circles and stars.

Table 1

Sample characteristics (N = 62).

Demographic characteristics		%
Age, years	43–81, mean 65, standard deviation 8	—
Gender	Female	48
Marital status	Married	69
Education	More than high school	47
Employment status	Employed	34
	Not currently working	39
	Other	27
Race	White non-Hispanic	85
	Black non-Hispanic	12
	Hispanic	3
Body mass index	20 to 45, mean 27, SD 6	—
	20 to <25 (normal range)	48%
	25 to <30 (overweight)	30%
	30 to 45 (obesity)	22%

Clinical characteristics		%
Recurrence of disease	Yes	23
Previous chemotherapy	Yes	39
Pre-concurrent chemoradiation therapy staging	I-II	19
	III	74
	IV	7
	—	—
Radiation technique	3-dimensional conformational radiation therapy (3D-CRT)	38
	intensity-modulated radiation therapy (IMRT)	62

Table 2
Mixed-effect modeling of weekly changes in the MDASI 15-symptom component score.

Effect	Estimate	SE	df	t	<i>p</i> [*]
Intercept	5.8266	2.2260	55	2.62	0.0114
Week 0	0	.	.	.	.
Week 1	0.09538	0.1539	569	0.62	0.5357
Week 2	0.1042	0.1752	569	0.59	0.5523
Week 3	0.3125	0.1859	569	1.68	0.0933
Week 4	0.4353	0.1908	569	2.28	0.0229
Week 5	0.7248	0.1976	569	3.67	0.0003
Week 6	0.9850	0.1973	569	4.99	<0001
Week 7	1.1648	0.1970	569	5.91	<0001
Week 8	1.1956	0.2091	569	5.72	<0001
Week 9	1.0916	0.2069	569	5.28	<0001
Week 10	0.9156	0.2025	569	4.52	<0001
Week 11	0.5016	0.2105	569	2.38	0.0175
Week 12	0.4518	0.2134	569	2.12	0.0347
Week 13	0.2127	0.2145	569	0.99	0.3219
Week 14	0.2248	0.2167	569	1.04	0.3001
Week 15	0.1416	0.2239	569	0.63	0.5276

MDASI: M. D. Anderson Symptom Inventory; SE: standard error; df: degrees of freedom.

Age, sex, race, BMI, recurrence of cancer, dose of radiotherapy, previous chemotherapy, and type of radiotherapy were adjusted. MDASI: M. D. Anderson Symptom Inventory; SE: standard error; df: degrees of freedom.

* Bold indicates a significant value.

Table 3

Changes in serum cytokines related to changes in symptom severity over eight weeks. of CXRT (estimate* (SE)).[†]

	Five most severe symptoms [‡]	All 15 symptoms	Esophagitis-related symptoms [‡]	Affective symptoms [‡]
Intercept	3.68 (3.34)	2.48 (2.51)	6.04 (2.87) [§]	5.94 (3.07)
Days of radiation therapy	0.03 (0.01) [¶]	0.02 (0.01) [¶]	0.04 (0.01) [¶]	0.005 (0.008)
sTNF-R1	1.51 (0.93)	1.74 (0.69) [§]	1.15 (1.02)	1.87 (1.00)
IL-1RA	-0.86 (0.68)	-0.34 (0.51)	-1.40 (0.81)	-0.38 (0.77)
IL-6	0.32 (0.16) [§]	0.09 (0.12)	0.77 (0.19) [¶]	-0.06 (0.19)
IL-8	-0.15 (0.14)	-0.10(0.11)	-0.49 (0.17) [¶]	-0.18 (0.16)
IL-10	0.65 (0.34)	0.42 (0.26)	0.43 (0.36)	-0.22 (0.36)
IL-12	0.19 (0.25)	0.01 (0.18)	0.17 (0.26)	0.02 (0.26)

CXRT: concurrent chemoradiation therapy; SE: standard error; sTNF-R1: soluble receptor 1 for tumor necrosis factor; IL: interleukin; RA: receptor antagonist.

[†] Age, sex, race, recurrence of cancer, dose of radiotherapy, BMI, previous chemotherapy, and type of radiotherapy were adjusted in all models.

[‡] The five most severe symptoms: pain, fatigue, lack of appetite, disturbed sleep, sore throat. Esophagitis-related symptoms: pain, sore throat. Affective symptoms: distress, sadness.

[§] $p < .05$.

[¶] $p < .01$.

^{¶¶} $p < .0001$.