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Preoperative inflammatory biomarkers and neurovegetative symptoms in peritoneal carcinomatosis patients

Carissa A. Low, **Dana H. Bovbjerg**, **Frank J. Jenkins**, **Steven A. Ahrendt**, **Haroon A. Choudry**, **Matthew P. Holtzman**, **Heather L. Jones**, **James F. Pingpank**, **Lekshmi Ramalingam**, **Herbert J. Zeh**, **Amer H. Zureikat**, and **David L. Bartlett**
University of Pittsburgh Cancer Institute

Abstract

Background—Inflammation plays a central role in peritoneal carcinomatosis (PC) etiology and progression, and circulating levels of inflammatory biomarkers prior to surgery predict progression-free and overall survival in PC patients. Depression and fatigue are prevalent among PC patients, and experimental research shows that these symptoms may be mediated by proinflammatory cytokines. As yet unstudied is the possibility that the heightened levels of inflammatory markers in PC patients may contribute to their experience of common neurovegetative symptoms.

Methods—Validated self-report measures of fatigue, depressive symptoms, and quality of life were administered to 64 patients scheduled to undergo aggressive surgical treatment for PC. Serum samples were collected the morning of surgery, and ELISAs were conducted to quantify circulating IL-6, CRP, and TNF-α levels.

Results—Consistent with hypotheses, higher IL-6 levels were associated with more severe fatigue ($\beta = -.39$, $p < .01$) and neurovegetative symptoms of depression ($\beta = .30$, $p < .05$). IL-6 was also related to poorer physical quality of life ($\beta = -.28$, $p < .05$). CRP showed similar significant relationships with fatigue and physical quality of life. Inflammatory biomarkers were not significantly related to emotional symptoms of depression or to emotional or social functioning aspects of quality of life, and TNF-α levels were not related to patient-reported measures.

Conclusion—Preoperative inflammatory activity may contribute to patients' experiences of fatigue and neurovegetative depressive symptoms as well as impaired quality of life. These biological mechanisms warrant consideration in the clinical management of neurovegetative symptoms in PC patients.

Correspondence regarding this article should be directed to Dr. Carissa A. Low, Biobehavioral Oncology Program, University of Pittsburgh Cancer Institute, 5115 Centre Avenue, Suite 140, Pittsburgh, PA 15232. lowca@upmc.edu.

Keywords

Sickness behavior; inflammation; cytokines; depression; fatigue; neurovegetative symptoms; quality of life; cancer; peritoneal carcinomatosis

1. Introduction

Peritoneal carcinomatosis (PC) is a common manifestation of metastatic gastrointestinal and gynecologic cancers as well as cancers such as mesothelioma and sarcoma. PC often presents as pain, ascites, and bowel obstruction caused by progressive seeding of tumor within the peritoneal cavity and is traditionally considered to be Stage IV metastatic disease. PC does not respond well to systemic therapy and has historically been viewed as a terminal condition with limited treatment options and median survival of 3–12 months (Gusani et al., 2008). Recent treatment advances, most notably aggressive cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CS + HIPEC), have led to significant improvements in prognosis (e.g., 40% five-year survival; Cashin et al., 2012). However, patients with PC commonly report significant impairments in quality of life (QoL), including elevated depressive symptoms and poor physical functioning (Hill et al., 2011; McQuellon et al., 2001). Inflammation plays a central role in PC etiology and progression (Lohani et al., 2013), and elevations in circulating levels of inflammatory biomarkers (i.e., CRP) have been noted in PC patients and are associated with progression-free and overall survival in this context (Chua et al., 2012; van de Poll et al., 2011).

In animal models, peripheral infusion or induction of inflammatory factors (e.g., IL-6) induce central nervous system changes leading to observable “sickness behaviors” (e.g., reduced physical activity and food intake; Dantzer et al., 2008; Schedlowski et al., 2014). Experimental studies with healthy human volunteers have demonstrated analogous effects on self-reported neurovegetative symptoms (e.g. fatigue, restless sleep, appetite changes; Miller et al., 2009; Schedlowski et al., 2014). As yet unstudied is the possibility that the heightened levels of circulating inflammatory markers in PC patients may contribute to the severity of their experience of neurovegetative symptoms.

Growing evidence links inflammatory markers to neurovegetative symptoms in the context of cancer (Low & Bovbjerg, 2014). Inflammatory cytokines caused by injected tumors induce sickness behaviors in animal models (Lamkin et al., 2011). In cancer patients, analogous neurovegetative symptoms often cluster together, suggesting a shared biological mechanism (Dantzer et al., 2012). Elevated inflammatory cytokine levels have been noted in cancer patients with depression, relative to cancer patients without depression (Musselman et al., 2001). When researchers have examined subgroups of depressive symptoms, neurovegetative (but not affective) depressive symptoms have been associated with circulating IL-6 levels in ovarian cancer patients (Lutgendorf et al., 2008) and palliative cancer patients (Inagaki et al., 2013). Associations between fatigue and proinflammatory cytokines are also well-documented (Bower & Lamkin, 2013; Saligan & Kim, 2012). However, the relationships between elevated inflammatory markers and neurovegetative symptoms have not yet been examined in PC patients.

Given published evidence that: (1) PC patients exhibit significant elevations in inflammatory markers; (2) inflammatory markers induce sickness behaviors and neurovegetative symptoms; and (3) many PC patients endorse significant neurovegetative symptoms, we posit that these symptoms may be mediated, in part, by inflammatory pathways. The goal of this study of PC patients was to test the hypothesis that higher preoperative inflammatory cytokine levels are related to more severe patient-reported neurovegetative symptoms, including neurovegetative depressive symptoms, fatigue, and poor physical QoL. We also examined associations between inflammatory markers and other dimensions of depression and QoL, such as emotional and social well-being.

2. Methods

2. 1 Participants

Data on patient-reported symptoms and serum samples were available from 64 patients who had surgery between March 2010 and December 2011. All patients were diagnosed with PC and scheduled to undergo aggressive cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Of note, steroid medications, chemotherapeutic medications, and other immunosuppressive agents are routinely held for four weeks or longer prior to PC surgery to minimize wound healing complications. Demographic and disease characteristics of the sample are displayed in Table 1. On average, participants were middle-aged, overweight, and about two years from their initial cancer diagnosis. Most participants were male, white, and diagnosed with appendiceal or colorectal cancer.

2.2 Procedure

Self-report measures were completed by patients prior to surgery, during their preoperative clinic visit. Blood samples were collected the morning of surgery, and ELISAs were conducted to quantify circulating IL-6, CRP, and TNF-α levels. Data on demographic variables, cancer diagnosis, and body mass index (BMI) were obtained from medical records. This study was approved by the University of Pittsburgh Institutional Review Board.

2.3 Measures

2.3.1 Depressive symptoms—The 20-item Center for Epidemiologic Studies – Depression Scale (CES-D; Radloff, 1977) was administered to assess depressive symptoms in the past week. Internal consistency for the total scale was adequate (α = .80). The CES-D also yields four subscales: neurovegetative symptoms (seven items, e.g., “I felt that everything I did was an effort”; α = .82 in this sample), negative affect (seven items, e.g., “I felt sad”; α = .82 in the current sample); positive affect (4 reverse-scored items; e.g., “I enjoyed life”; α = .69 in this sample), and interpersonal symptoms (2 items, e.g., “People were unfriendly”; α = .63 in this sample).

2.3.2 Fatigue—The 13-item Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) subscale was used to measure fatigue in the past week (Yellen et al., 1997). The FACIT-F has been validated in patients with cancer and shows good reliability, validity, and internal consistency (α = .85 in the current sample). Higher scores represent less fatigue.

2.3.3 Quality of life—The 27-item Functional Assessment of Cancer Therapy (FACT, version 4; Cella et al., 1993) is widely used to assess health-related QoL among patients with cancer. The FACT consists of four subscales: physical well-being (seven items, e.g., "I feel ill"; $\alpha = .87$ in this sample), social/family well-being (seven items, e.g., "I get emotional support from my family"; $\alpha = .70$ in this sample), emotional well-being (six items, e.g., "I feel sad"; $\alpha = .68$), and functional well-being (seven items, e.g., "I am able to work"; $\alpha = .86$). Higher scores reflect better QoL in the past week.

2.3.4 Inflammatory markers—Serum samples were stored at −80°C until analysis in batches. IL-6, CRP, and TNF-α levels were determined using a high sensitivity quantitative sandwich enzyme immunoassay kit (R & D Systems). Biomarker values were extrapolated from a standard curve with linear regression from a log-linear curve. All samples were run in duplicate and the average intra-assay coefficients of variation ranged from 6–7%. Even after 1:2000 dilution, there were three outliers falling outside of the standard curve for CRP; these outlying values were dropped from analyses. Natural log transformation was applied to normalize raw score distributions of the IL-6 and CRP values.

2.3.5 Data analysis—Descriptive statistics on patient-reported and inflammatory measures were conducted. Primary analyses were hierarchical multiple regressions on depressive symptoms (total score and subscales), fatigue, and quality of life (total score and subscales), in separate models. Two blocks of predictors were entered: covariates; followed by inflammatory biomarkers (i.e., IL-6, CRP, and TNF-α in separate models). Sample sizes vary slightly across analyses due to missing data on some measures for some participants.

To identify covariates, bivariate associations between patient-reported and inflammatory measures and demographic (i.e., age, sex, race) and medical (i.e., BMI, time since diagnosis, diagnosis) were examined. The only significant relationships ($p < .05$) that emerged were between patient age and some patient-reported measures (e.g., older participants reported less negative affective symptoms of depression, better emotional well-being quality of life, and better overall quality of life) and between having mesothelioma and both patient-reported outcomes and IL-6. Age and diagnosis were therefore included as covariates in all analyses.

3. Results

Depression and fatigue were common, with 28% of patients endorsing clinically significant levels of depressive symptoms (CESD ≥ 16) and 32% endorsing significant fatigue (FACT-Fatigue ≤35) prior to surgery. Quality of life scores (FACT) were within the range noted by previous studies of PC patients (e.g., 79.5 in Hill et al.,2011; 81.2 in Ihemeldandu et al., 2013; 89.9 in McQuellon et al., 2001; 73.1 in Tuttle et al., 2006). Consistent with the role of inflammation in PC, average IL-6 levels detected via R & D ELISA were higher than levels observed in middle-aged adults at risk for cardiovascular disease (Pai et al., 2004) but lower than levels observed in preoperative ovarian cancer patients (Lutgendorf et al., 2008).

After adjusting for patient age and diagnosis, higher IL-6 levels were associated with significantly more severe neurovegetative symptoms of depression ($\beta = .30$, $p < .05$, $\Delta R^2 = .$

075), worse physical QoL (β = −.28, p < .05, ΔR^2 = .066), and greater fatigue (β = −.39, p < .01, ΔR^2 = .12). Similar associations were found between CRP and physical QoL (β = −.30, p < .05, ΔR^2 = .084 and fatigue (β = −.29, p < .05, ΔR^2 = .081). TNF-α levels were not related to any of the patient-reported measures. None of the inflammatory markers were related to affective symptoms of depression, or to emotional or social aspects of QoL. Standardized regression coefficients for all tested models are displayed in Table 2.

4. Discussion

Neurovegetative symptoms, including significant depressive symptoms and fatigue, are common among PC patients prior to surgery and are related to poor patient QoL. As hypothesized, preoperative serum IL-6 and CRP levels were significantly associated with greater sickness behavior symptoms, including greater fatigue and worse physical quality of life (e.g., feeling ill, having pain). Higher IL-6 levels were also related to more severe neurovegetative symptoms of depression (e.g., poor appetite, restless sleep, trouble concentrating, and lack of motivation). Although depressive symptoms were common, with 28% of patients endorsing clinically significant depression, overall depressive symptoms were not significantly related to inflammatory activity. Consistent with previous research in other cancer populations (e.g., Lutgendorf et al., 2006), neither affective symptoms of depression, nor interpersonal symptoms of depression were related to levels of inflammatory markers. Social, emotional, and functional aspects of QoL were also unrelated to inflammatory marker levels. These results highlight the value of examining specific subscales of patient-reported QoL outcomes.

Findings support a role of inflammation in neurovegetative symptoms of depression and fatigue in this patient population but suggest that different mechanisms may underlie the more affective symptoms of depression and aspects of QoL (e.g., feeling sad, worried, guilty). These affective symptoms may also more closely reflect psychological responses to the stress of living with cancer rather than being driven by physiological responses to cancer. These distinct dimensions of depression may require distinct treatment strategies; for example, affective symptoms may be more responsive to cognitive-behavioral intervention than neurovegetative symptoms.

Given the correlational nature of the current study, it is not possible to establish a causal relationship between proinflammatory markers and neurovegetative symptoms. However, findings are consistent with experimental studies demonstrating that inflammatory activation induces sickness symptoms/behaviors in animals and healthy humans (Reichenberg et al., 2001; Schedlowski et al., 2014). Inflammatory pathways may thus represent a potential target of novel interventions to reduce neurovegetative symptoms in these patients. Unlike affective symptoms, neurovegetative symptoms of depression have been shown in previous studies to be unresponsive to traditional antidepressant treatments (Capuron et al., 2002), and there is limited empirical support for pharmacological treatments for fatigue in cancer patients (Minton et al., 2010).

Limitations of the current study include the relatively small sample size, cross-sectional design, and lack of data on some potential covariates including medications and

comorbidities. Nevertheless, this study demonstrates that inflammatory processes are associated with heightened neurovegetative symptoms in PC patients and contributes to our growing scientific understanding of the relationships between immune activation and subjective patient experiences associated with cancer diagnosis and treatment. Prospective longitudinal research and randomized clinical trials are needed to elucidate causal relationships between cytokines and symptoms in patients undergoing treatment for cancer (Low & Bovbjerg, 2014). In addition, innovative intervention strategies are needed to more effectively manage neurovegetative symptoms in PC and other cancer patients and to minimize their pernicious impact on quality of life.

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Table 1

Characteristics of the sample (n = 64)

Variable	Mean ± SD (range) or %
Age (years)	54.55 ± 11.92 (18–78)
Sex	67% male
Race	93% white
Body Mass Index	27.00 ± 5.02 (17.5 – 44.6)
Diagnosis	53% appendiceal cancer; 36% colorectal cancer; 6% mesothelioma; 5% other
Time since diagnosis	1.98 years ± 1.84 years (32 days – 9.30 years)
Depressive Symptoms (CESD)	11.63 ± 7.72 (0–32)
Neurovegetative symptoms	4.49 ± 3.95 (0–16)
Negative affective symptoms	3.23 ± 3.22 (0–12)
Positive affective symptoms	3.68 ± 3.17 (0–12)
Interpersonal symptoms	0.23 ± 0.76 (0–4)
Fatigue (FACT-Fatigue)	37.97 ± 11.29 (0–52)
QOL (FACT)	85.44 ± 14.90 (41–106)
PWB	22.19 ± 5.79 (2–28)
SWB	25.06 ± 2.98 (16–28)
EWB	17.49 ± 4.15 (7–24)
FWB	20.80 ± 5.79 (3–28)
IL-6 (pg/mL)	5.10 ± 4.94 (0.47–20.69)
TNF-α (pg/mL)	5.79 ± 1.72 (3.15–13.19)
CRP (mg/L)	15.00 ± 21.93 (0.17–90.31)

Table 2

Standardized beta coefficients for inflammatory biomarkers regressed on patient-reported outcomes, adjusted for patient age and diagnosis.

	IL-6	CRP	TNF-α
CES-D Total	.18	.21	−.10
Neurovegetative	.30*	.20	−.06
Negative affect	.23	.19	−.18
Positive affect	−.11	.11	.02
Interpersonal	−.17	−.14	.02
FACT	−.18	−.22†	−.04
Physical	−.28*	−.30*	−.14
Functional	−.24†	−.25†	−.06
Social	.05	−.07	.05
Emotional	.00	−.01	.11
FACIT-Fatigue	−.39**	−.29*	−.02

† p < .10;

* p < .05;

** p < .01