The Oncologist®

Symptom Management and Supportive Care

The Systemic Inflammatory Response and Its Relationship to Pain and Other Symptoms in Advanced Cancer

BARRY J. LAIRD,[a,b] DONALD C. MCMILLAN,[c] PETER FAYERS,[a] KENNETH FEARON,[b] STEIN KAASA,[a] MARIE T. FALLON,[b] PÅL KLEPSTAD[a,d,e]

[a]European Palliative Care Research Centre, Norwegian University of Science and Technology, Trondheim, Norway; [b]University of Edinburgh, Edinburgh, Scotland, United Kingdom; [c]University of Glasgow, Glasgow, Scotland, United Kingdom; [d]Department of Anaesthesia and Acute Medicine, St. Olav University Hospital, Trondheim, Norway; [e]Department of Circulation and Medical Imaging, Medical Faculty, Norwegian University of Science and Technology, Trondheim, Norway

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Symptoms • Inflammation • Cancer

ABSTRACT

Introduction. Inflammation has been identified as a hallmark of cancer and may be necessary for tumorgenesis and maintenance of the cancer state. Inflammation-related symptoms are common in those with cancer; however, little is known about the relationship between symptoms and systemic inflammation in cancer. The aim of the present study was to examine the relationship between symptoms and systemic inflammation in a large cohort of patients with advanced cancer.

Methods. Data from an international cohort of patients with advanced cancer were analyzed. Symptoms and patient-related outcomes were recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core Questionnaire. Systemic inflammation was assessed using C-reactive protein levels. The relationship between these symptoms and systemic inflammation was examined using Spearman rank correlation (ρ) and the Mann-Whitney *U* test.

Results. Data were available for 1,466 patients across eight European countries; 1,215 patients (83%) had metastatic disease at study entry. The median survival was 3.8 months (interquartile range [IQR] 1.3–12.2 months). The following were associated with increased levels of inflammation: performance status ($\rho = .179$), survival ($\rho = .347$), pain ($\rho = .154$), anorexia ($\rho = .206$), cognitive dysfunction ($\rho = .137$), dyspnea ($\rho = .150$), fatigue ($\rho = .197$), physical dysfunction ($\rho = .207$), role dysfunction ($\rho = .176$), social dysfunction ($\rho = .132$), and poor quality of life ($\rho = .178$). All were statistically significant at $p < .001$.

Conclusion. The results show that the majority of cancer symptoms are associated with inflammation. The strength of the potential relationship between systemic inflammation and common cancer symptoms should be examined further within the context of an anti-inflammatory intervention trial.

The Oncologist 2013;18:1050–1055

Implications for Practice: Symptoms are often regarded as natural sequelae in advanced cancer, resulting usually from tumor load. Here the role of systemic inflammation in symptom genesis in cancer is explored. Pro-inflammatory cytokines have been demonstrated to have a role in animal models of symptom development (e.g., cytokine-induced sickness behavior). This study of a large international cohort of patients with advanced cancer shows that key symptoms may in part be the result of systemic inflammation (mediated by interleukin-6). These findings may potentially influence practice by providing a new approach to symptom management in which systemic inflammation is realized as a key therapeutic target.

INTRODUCTION

Inflammation and cancer are linked inextricably. Mantovani et al. described inflammation as the seventh hallmark of cancer: it is needed for cancer to develop but also for maintenance of the cancer state [1]. Work to date has suggested that pre-existing inflammatory states may play a role in carcinogenesis of some tumor types (e.g., inflammatory bowel disease leading to colon cancer) and that treatment with anti-inflammatory medication may reduce the mortality rate from other cancers [2].

Less is known, however, about the relationship between cancer symptoms and inflammation. While tumor development and progression are occurring, symptoms are the physical and psychological manifestations of the underlying cancer. Pain is the most common cancer symptom and has been shown to be related to systemic inflammation [3]. However, symptoms rarely exist in isolation, with pain, fatigue, lack of energy, weakness, and appetite loss occurring in more than 50% of those with cancer [4].

Our group has explored patient symptoms further by examining the relationship between symptoms, termed "symptom clusters"; that is, three or more concurrent symptoms

Correspondence: Barry Laird, M.D., Edinburgh Cancer Research Centre, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, United Kingdom. Telephone: 00-44-131-777-3504; Fax: 00-44-131-777-3564; E-Mail: barry.laird@ed.ac.uk Received April 4, 2013; accepted for publication July 1, 2013; first published online in ***The Oncologist*** *Express* on August 21, 2013. http://dx.doi.org/10.1634/theoncologist.2013-0120

that are related to each other [5, 6]. Pain, depression, and fatigue were shown to be the basis of a symptom cluster in combination with reduced physical function in patients with cachexia [5]. This work demonstrated that symptoms do not simply coexist but can seemingly exacerbate one another, demonstrating the multiplicative role symptoms may have. This cluster effect has been compared with the pro-inflammatory-driven cytokine-induced sickness behavior seen in animal models. However, currently the role of systemic inflammation in the genesis of multiple cancer symptoms is not understood [7].

The aim of the present study was to examine the relationship of pain, other key symptoms, and systemic inflammation in a large international cohort of patients with advanced cancer.

Materials and Methods

Study Design

An analysis was undertaken on an international biobank of patients with advanced cancer [8]. These data were collected between 2005 and 2008 across multiple centers (e.g., hospital inpatients, hospital outpatients, hospices/specialist palliative care units) in eight European countries. A convenience sample was taken from the various study centers in patients who had a diagnosis of cancer, who were more than 18 years of age, and who were receiving a strong opioid medication for cancer pain (as defined by the World Health Organization analgesic ladder for cancer pain relief) [9]. Ethical approval was given for the primary data collection, and all patients provided written informed consent.

Data Collection

The following data were collected and analyzed: patient demographics, site of primary disease, and presence of metastases. Pain, other symptoms, and patient-reported outcomes were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core Questionnaire (EORTC QLQ—C30) [10]. Inflammation was measured using C-reactive protein (CRP), which has been widely validated as a biomarker of systemic inflammation. CRP was taken by venous blood sample at study entry and analyzed at a central laboratory; the limit of detection was 5 mg/L^{-1}. CRP levels were grouped into normal ($\leq$ 10 mg/L^{-1}) and elevated ($>$ 10 mg/L^{-1}) categories.

Statistical Analysis

The EORTC QLQ-C30 was scored according the EORTC scoring manual [11]. Higher scores correspond to better health-related quality of life in the function scales and the global quality-of-life scale, whereas higher scores in symptom scales and items represented more troublesome symptoms. Karnofsky performance status was converted to Eastern Oncology Cooperative Group (ECOG) performance status to simplify analysis and interpretation [12]. Clinicopathological factors were studied as they related to increasing levels of systemic inflammation, using CRP levels. CRP levels were examined both as a continuous variable and grouped according to normal and elevated categories described above.

Statistical testing was carried out at the 5% level; therefore, 95% confidence intervals are reported. The associations between EORTC factors and CRP were examined using Spearman rho-rank correlations; the large sample size (n = 1,466) meant that any correlation $>$ .086 was highly statistically significant ($p < .001$). EORTC factors and CRP levels for patients with normal CRP levels ($\leq$ 10 mg/L^{-1}) were compared with those of patients with elevated CRP levels ($>$ 10 mg/L^{-1}) using Mann-Whitney *U* tests. All analysis was undertaken using SPSS version 18.0 (SPSS, Chicago, IL, http://www.spss.com). Unless otherwise stated, Medians and Interquartile Range (IQR) is used.

Results

Data were available for 1,466 patients from eight countries. Patient demographics and performance status are shown in Table 1. Half of patients (50%) were men, and the median age was 62 years (IQR 54–70 years). All patients had cancer: 1,215 patients (83%) had metastatic disease and the remainder had locally advanced disease. The most common primary tumor types were gastroesophageal (19%), pulmonary (17%), and breast (15%) cancers. At the time of study entry, patients were being treated in oncology wards (680 patients [46%]), hospices/specialist palliative care units (449 patients [31%]), outpatient clinics (304 patients [21%]), and surgical wards (33 patients [2%]). All patients were receiving strong opioid analgesia as defined by the World Health Organization analgesic ladder for cancer pain relief [9]. The median survival was 3.83 months (IQR 1.33–12.17 months). The median performance status (ECOG) was 2 (interquartile range 2–3).

The relationship between the inflammatory response (measured using CRP) and pain and other factors is shown in Table 2. The following were associated with increasing levels of systemic inflammation: performance status ($\rho = .179$), survival ($\rho = .347$), pain ($\rho = .154$), anorexia ($\rho = .206$), cognitive dysfunction ($\rho = .137$), dyspnea ($\rho = .150$), fatigue ($\rho = .197$), physical dysfunction ($\rho = .207$), role dysfunction ($\rho = .176$), social dysfunction ($\rho = .132$), and poor quality of life ($\rho = .178$). Emotional function, nausea/vomiting, diarrhea, sleep disturbances, and constipation were not significantly associated with inflammation. When CRP levels were divided into those greater than 10 mg/L^{-1} and those less than or equal to 10 mg/L^{-1}, we obtained an almost identical number of highly significant factors for both categories.

Further analysis was undertaken to compare differences among patients in different places of care and among the largest tumor groups. With the exception of the group who were surgical inpatients (n = 33), correlations remained similar among patients in palliative care units, those in oncology wards, and those receiving care as outpatients, with the exception of pain and cognitive function in the outpatient cohort ($p < .05$). In patients with pulmonary (n = 244) and gastroesophageal cancer (n = 274), correlations that were significant in the sample as a whole were also significant for these groups, with the exception of dyspnea ($p < .05$).

Discussion

These findings demonstrate that pain and other symptoms and patient-reported outcomes are correlated with systemic inflammation, as measured using CRP, in patients with cancer. Increasing levels of systemic inflammation were associated with worse symptoms and worse patient-reported outcomes.

Table 1. Demographics (n = 1,466)

Parameter	*n*	% of patients
Age (years)		
≤ 65	859	14
65–74	395	27
≥ 74	212	59
Sex		
Male	739	50
Female	727	50
Country		
Switzerland	103	7
Germany	96	7
Denmark	9	1
United Kingdom	276	19
Iceland	142	10
Italy	298	20
Norway	430	29
Sweden	112	8
Primary cancer diagnosis		
Breast	212	15
Urological	98	7
Gynecological	113	8
Prostate	180	12
Gastroesophageal	274	19
Hematological	85	6
Head and neck	75	5
Pancreaticobiliary	32	2
Pulmonary	244	17
Others	153	10
Performance status KPS (ECOG)		
100–80 (1)	365	25
70–60 (2)	607	41
50–40 (3)	398	27
30–10 (4)	96	7

Abbreviations: ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status.

Although the overall correlations are low, they are statistically significant in the context of the large sample size. Our group has previously described the relationship between pain and inflammation in cancer, and the current findings support this [13]. Furthermore, evidence of an association between other factors and inflammation has been shown. Although the findings do not demonstrate causality, they do indicate an association between inflammation and symptoms in cancer. To our knowledge, this is the first study of this kind to demonstrate the relationship between inflammation and multiple symptoms in advanced cancer.

Previous basic science and clinical work in cancer has tended to focus on the relationship between symptoms in isolation and inflammation. The findings presented here support previous work but expand on this by highlighting the idea that multiple symptoms are related to systemic inflammation.

Pain as a core component of inflammation was first described by Celsus (177 A.D.), and basic science research has provided some explanation. Pro-inflammatory cytokines cause pain by various means, including spontaneous nerve fiber discharge [14], alteration of neurotransmission [15], and changes to the phenotype of nerve ending receptors [16]. In addition, animal models of hyperalgesia (exaggerated pain response) suggest that the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) are also related to increased pain. In the clinical setting, the relationship between CRP (as a surrogate of IL-6) and pain has been shown in cancer [3].

Increasing numbers of studies of cancer fatigue and its relationship to inflammation are being performed. It has been found that patients with breast cancer who have fatigue have increased levels of pro-inflammatory cytokines, including IL-6 and IL-1RA [17]. It has also been shown that the pro-inflammatory cytokines interferon-α (IFN-α) and IL-2), which are used in the treatment of cancer, can cause fatigue and depression [18, 19]. In contrast, agents that modulate the inflammatory response may improve fatigue. Patients with cancer who were given etanercept (TNF-α decoy receptor) in combination with docetaxel had less fatigue than those who received docetaxel alone [20]. In patients with Castleman disease (IL-6 driven), the administration of IL-6 antibodies resulted in reduced levels of fatigue [21].

Patients with low levels of physical activity have higher levels of pro-inflammatory cytokines, whereas exercise has been shown to reduce fatigue in those with nonmalignant disease and in those with cancer [22, 23]. The exact mechanisms for this are unclear in patients with cancer, but there is a growing body of work examining possible causal factors [23].

Mood disorders are also associated with inflammation in cancer. Patients with depression have increased levels of IL-6 [24, 25], whereas cognitive impairment has been associated with systemic inflammation. Patients who are being treated with immunotherapy for chronic myeloid leukemia have been shown to have increased levels of cognitive impairment [26].

Cancer treatment can also affect the pro-inflammatory response. Radiotherapy results in the activation of the immune system, causing the release of pro-inflammatory cytokines, which can cause both acute and chronic radiation damage [27]. Tumor growth factor-β1 (TGF-β1) is implicated in radiation-induced pro-inflammatory responses and may result in increased levels of radiotherapy-related damage [28, 29]. Chemotherapy results in cancer cell death, which in turn results in immunogenic antigen release and the cell-mediated immune response. Paclitaxel causes increased levels of IL-6, IL-8, and IL-10, which cause joint pain and flulike symptoms [30]. Docetaxel [31], gemcitabine [32], cisplatin [33], etoposide [34], and bleomycin [35] have also been shown to initiate the inflammatory response, with resulting symptoms. Some chemotherapy agents activate nuclear factor-κB (NF-κB), which causes activation of the N-methyl D aspartate receptor and production of substance P, resulting in hyperalgesia [36]. This would suggest that some anticancer treatments may also fuel the fire of inflammation in cancer. The effects of chemotherapy on inflammation, however, may be more a result of the direct effect on immune cells (e.g., tumor-associated macrophages), and this effect can vary widely among cytotoxic agents [37]. Inflammation may also interfere with drug metabolism [38]. Anticancer therapies modulate inflammation in various ways. Continued research in this area will allow a

Table 2. Relationship between CRP and pain and other factors in patients with advanced cancer

Factor	Correlation[a] ρ	*p* value	CRP ≤ 10 mg/L^{-1} (n = 445) Mean (SD)	CRP > 10 mg/L^{-1} (n = 1,021) Mean (SD)	*p* value[b]
Age (years) ≤ 65/65–74/≥ 74	0.048	.069	61.6 (12.4)	61.3 (11.9)	.564
Performance status (ECOG 0–1/2/3/4)	0.179	<.001	1.94 (0.85)	2.24 (0.86)	<.001
Survival (months)	0.347	<.001	13.6 (12.68)	6.9 (10.0)	<.001
EORTC QLQ-C30 Factor					
Pain	0.154	<.001	56.5 (28.9)	63.2 (27.9)	<.001
Appetite loss	0.206	<.001	38.5 (35.6)	51.9 (36.6)	<.001
Cognitive function	0.137	<.001	68.6 (26.7)	64.4 (27.1)	.004
Dyspnea	0.150	<.001	26.9 (30.6)	34.6 (34.7)	<.001
Fatigue	0.197	<.001	58.5 (25.1)	65.8 (24.7)	<.001
Physical function	−0.207	<.001	46.6 (26.5)	37.7 (25.5)	<.001
Role function	−0.176	<.001	33.2 (32.7)	24.4 (28.5)	<.001
Emotional function	−0.064	.014	68.6 (25.0)	66.3 (25.4)	.070
Social function	−0.132	<.001	51.4 (33.3)	44.4 (32.3)	<.001
Quality of life	−0.178	<.001	44.1 (23.9)	38.0 (22.9)	<.001
Nausea/vomiting	0.085	.001	21.2 (27.0)	24.8 (28.2)	.012
Diarrhea	0.039	.132	15.9 (27.9)	18.1 (29.3)	.186
Sleep	0.058	.028	32.9 (32.7)	33.7 (33.7)	.833
Constipation	0.011	.684	43.5 (37.2)	44.2 (37.3)	.741

[a]Spearman rank correlation.
[b]Mann-Whitney *U* test. Note that *p* values for Spearman rank correlation and Mann-Whitney *U* test are not identical.
Abbreviations: CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core Questionnaire.

greater understanding of this process and how it can be modulated to optimize treatment.

Clearly, examining inflammation and its relation to symptoms is challenging in cancer. However, it has been suggested that cancer symptoms may share a similar biological mechanism and rather than systemic inflammation being the cause for individual symptoms, inflammation may be implicated in the genesis of multiple cancer symptoms, similar to the relation of cytokine-induced sickness behavior in animal models [39]. Researchers creating animal models of cytokine-induced sickness behavior have concentrated on cachexia and have confirmed the role of pro-inflammatory cytokines in cachexia development. Although this hypothesis is now a decade old, until recently, there has been little work examining the modulation of symptoms by attenuation of the inflammatory response. Whereas the role of systemic inflammation in the development of some cancer symptoms seems established, addressing the modulation of symptoms by reduction of the inflammatory response may seem daunting. Nevertheless, the work in cancer cachexia provides grounds for optimism.

Cachexia has systemic inflammation at its core; however, exercise or the administration of eicosapentaenoic fatty acid supplements or celecoxib (all proven anti-inflammatory interventions) has each been studied in isolation and has been shown to improve outcome in cachexia. A trial is now underway (EudraCT 2010−022897-14) examining these entities in combination (multimodal intervention) to prevent cancer cachexia [40]. This novel approach, whereby inflammation is targeted with the aim of preventing or delaying symptoms, may provide a platform on which to base future work [41–43].

A study by Temel and coworkers also highlighted the importance of optimal symptom control in improving survival in patients with cancer [44]. Combining optimal symptom control with anti-inflammatory therapies would be a novel approach in the treatment of cancer symptoms [42].

Further delineation is needed to establish whether certain cytokines are responsible for individual symptoms or whether multiple cytokines are responsible for combinations of symptoms [39]. Recent work with humanized antibody to IL-6 (ALD518) in non-small cell lung cancer demonstrated that ALD518 improved fatigue, lean body mass, and general symptoms [45]. Whether future anti-inflammatory therapies will be symptom specific, will target clusters of symptoms, or will attempt to attenuate a spectrum of symptoms is still to be established.

The lack of a control group is a limitation in the current study. The other main limitation is the low overall correlation between inflammation and symptoms. However, examining the relationship between inflammation and symptoms in cancer is challenging. As discussed, inflammation can vary according to the type of anticancer treatment used; however, details on specific therapies were not available, which is a limitation. Tumor load, coexisting infection, and other factors can also affect inflammation. Symptoms, on the other hand, can be modified by treatments (surgery, invasive procedures) or attenuated by medication. Furthermore, all patients in the study were receiving strong opioid medications, which can also affect inflammation [46]. This "background noise" makes examining inflammation and symptoms challenging, and it is therefore of interest that even in the presence of factors that could affect inflammation and symptoms, evidence of an association was shown.

Conclusion

The findings presented suggest an association between systemic inflammation and multiple cancer symptoms. This supports the growing body of basic science work in the area. The management of cancer symptoms is usually a reactive approach—treating symptoms once they have developed. A novel approach to symptom control in cancer would be to prevent symptoms. This would put prevention of symptoms at the center of cancer care rather than at the end—waiting until symptoms develop and trying to treat them. Studies that target the pro-inflammatory response with the aim of prevention of key symptoms are awaited with interest.

Acknowledgments

The biobank data collection was funded by the Norwegian Research Council and the European Union's 6th Framework (Contract 037777). Marie T. Fallon and Pål Klepstad served as joint senior authors on this paper.

Disclosures

Pål Klepstad: Ferrer Phrama (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Author Contributions

Conception/Design: Barry J. Laird, Donald C. McMillan
Provision of study material or patients: Stein Kaasa, Pål Klepstad
Collection and/or assembly of data: Barry J. Laird, Stein Kaasa, Pål Klepstad
Data analysis and interpretation: Barry J. Laird, Donald C. McMillan, Peter Fayers, Marie T. Fallon
Manuscript writing: Barry J. Laird, Donald C. McMillan, Peter Fayers, Ken Fearon, Stein Kaasa, Marie T. Fallon, Pål Klepstad
Final approval of manuscript: Barry J. Laird, Donald C. McMillan, Peter Fayers, Ken Fearon, Stein Kaasa, Marie T. Fallon, Pål Klepstad

References

1. Mantovani A, Allavena P, Sica A et al. Cancer-related inflammation. Nature 2008;454:436–444.

2. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA 2009;302:649–658.

3. Laird BJ, Scott AC, Colvin LA et al. Cancer pain and its relationship to systemic inflammation: An exploratory study. Pain 2011;152:460–463.

4. Teunissen SC, Wesker W, Kruitwagen C et al. Symptom prevalence in patients with incurable cancer: A systematic review. J Pain Symptom Manage 2007;34:94–104.

5. Laird BJ, Scott AC, Colvin LA et al. Pain, depression, and fatigue as a symptom cluster in advanced cancer. J Pain Symptom Manage 2011;42:1–11.

6. Dodd MJ, Miaskowski C, Lee KA. Occurrence of symptom clusters. J Natl Cancer Inst Monogr 2004; 32:76–78.

7. Cleeland CS, Bennett GJ, Dantzer R et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. Cancer 2003;97: 2919–2925.

8. Kurita GP, Sjogren P, Ekholm O et al. Prevalence and predictors of cognitive dysfunction in opioid-treated patients with cancer: A multinational study. J Clin Oncol 2011;29:1297–1303.

9. Ventafridda V, Tamburini M, Caraceni A et al. A validation study of the WHO method for cancer pain relief. Cancer 1987;59:850–856.

10. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–376.

11. Fayers PM, Aaronson NK, Bjordal K et al. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels, Belgium: European Organization for Research and Treatment of Cancer, 2001.

12. Ma C, Bandukwala S, Burman D et al. Interconversion of three measures of performance status: An empirical analysis. Eur J Cancer 2010;46:3175–3183.

13. Laird BJA, Scott AC, Colvin LA, McKeon A, Murray GD, Fearon KCH, Fallon MT. Cancer Pain and its Relationship to Systemic Inflammation: An Exploratory Study. Pain. 2011;152:460–463.

14. Oh SB, Tran PB, Gillard SE et al. Chemokines and glycoprotein120 produce pain hypersensitivity by directly exciting primary nociceptive neurons. J Neurosci 2001;21:5027–5035.

15. Eliav E, Herzberg U, Ruda MA et al. Neuropathic pain from an experimental neuritis of the rat sciatic nerve. Pain 1999;83:169–182.

16. Neumann S, Doubell TP, Leslie T et al. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. Nature 1996;384:360–364.

17. Schubert C, Hong S, Natarajan L et al. The association between fatigue and inflammatory marker levels in cancer patients: A quantitative review. Brain Behav Immun 2007;21:413–427.

18. Trask PC, Esper P, Riba M et al. Psychiatric side effects of interferon therapy: Prevalence, proposed mechanisms, and future directions. J Clin Oncol 2000;18:2316–2326.

19. Scheibel RS, Valentine AD, O'Brien S et al. Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. J Neuropsychiatry Clin Neurosci 2004;16:185–191.

20. Monk JP, Phillips G, Waite R et al. Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. J Clin Oncol 2006; 24:1852–1859.

21. Nishimoto N, Kanakura Y, Aozasa K et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 2005;106:2627–2632.

22. Mustian KM, Morrow GR, Carroll JK et al. Integrative nonpharmacologic behavioral interventions for the management of cancer-related fatigue. Oncologist 2007;12 Suppl 1:52–67.

23. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol 2005;98: 1154–1162.

24. Musselman DL, Miller AH, Porter MR et al. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: Preliminary findings. Am J Psychiatry 2001;158:1252–1257.

25. Dantzer R. Cytokine-induced sickness behaviour: A neuroimmune response to activation of innate immunity. Eur J Pharmacol 2004;500:399–411.

26. Pavol MA, Meyers CA, Rexer JL et al. Pattern of neurobehavioral deficits associated with interferon alfa therapy for leukemia. Neurology 1995;45:947–950.

27. Muller K, Meineke V. Radiation-induced alterations in cytokine production by skin cells. Exp Hematol 2007;35:96–104.

28. Quarmby S, Fakhoury H, Levine E et al. Association of transforming growth factor beta-1 single nucleotide polymorphisms with radiation-induced damage to normal tissues in breast cancer patients. Int J Radiat Biol 2003;79:137–143.

29. Madani I, De Ruyck K, Goeminne H et al. Predicting risk of radiation-induced lung injury. J Thorac Oncol 2007;2:864–874.

30. Pusztai L, Mendoza TR, Reuben JM et al. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. Cytokine 2004;25:94–102.

31. Tsavaris N, Kosmas C, Vadiaka M et al. Immune changes in patients with advanced breast cancer undergoing chemotherapy with taxanes. Br J Cancer 2002;87:21–27.

32. Plate JM, Plate AE, Shott S et al. Effect of gemcitabine on immune cells in subjects with adenocarcinoma of the pancreas. Cancer Immunol Immunother 2005;54:915–925.

33. Zhang B, Ramesh G, Norbury CC et al. Cisplatin-induced nephrotoxicity is mediated by tumor necrosis factor-alpha produced by renal parenchymal cells. Kidney Int 2007;72:37–44.

34. Wood LJ, Nail LM, Perrin NA et al. The cancer chemotherapy drug etoposide (VP-16) induces pro-inflammatory cytokine production and sickness behavior-like symptoms in a mouse model of cancer chemotherapy-related symptoms. Biol Res Nurs 2006;8:157–169.

35. Sime PJ, O'Reilly KM. Fibrosis of the lung and other tissues: New concepts in pathogenesis and treatment. Clin Immunol 2001;99:308–319.

36. Lieb K, Fiebich BL, Berger M et al. The neuropeptide substance P activates transcription factor NF-kappa B and kappa B-dependent gene expression in human astrocytoma cells. J Immunol 1997; 159:4952–4958.

37. De Palma M, Lewis CE. Macrophage regulation of tumor responses to anticancer therapies. Cancer Cell 2013;23:277–286.

38. Chua W, Clarke SJ, Charles KA. Systemic inflammation and prediction of chemotherapy

outcomes in patients receiving docetaxel for advanced cancer. Support Care Cancer 2013;20: 1869–1874.

39. Lee BN, Dantzer R, Langley KE et al. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. Neuroimmunomodulation 2004; 11:279–292.

40. Fearon KC. Cancer cachexia: Developing multimodal therapy for a multidimensional problem. Eur J Cancer 2008;44:1124–1132.

41. Fearon K, Strasser F, Anker SD et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol 2011;12: 489–495.

42. MacDonald N. Cancer cachexia and targeting chronic inflammation: A unified approach to cancer treatment and palliative/supportive care. J Support Oncol 2007;5:157–162.

43. Macdonald N. Terminology in cancer cachexia: Importance and status. Curr Opin Clin Nutr Metab Care 2012;15:220–225.

44. Temel JS, Greer JA, Muzikansky A et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733–742.

45. Rigas JR, Schuster SV, Orlov B et al. Effect of ALD518, a humanized anti-IL6 antibody, on lean body mass and symptoms in patients with advanced non-small cell lung cancer (NSCLC): Results of a phase II randomized, double-blind safety and efficacy trial. J Clin Oncol 2010;28:7622.

46. Walker JS. Anti-inflammatory effects of opioids. Adv Exp Med Biol 2003;521:148–160.