Anaemia and Other Predictors of Fatigue Among Patients on Palliative Therapy for Advanced Cancer

A. LATVALA, K. SYRJÄNEN, H. SALMENOJA and E. SALMINEN

Department of Oncology and Radiotherapy, Turku University Hospital, P.O.B. 52, FI-20521 Turku, Finland

Abstract. *The association of anaemia and other predictors of fatigue was studied in cancer patients on palliative treatment. A cohort of 128 consecutive patients (61 men and 67 women, mean age 63.6 years; range 36-85) was interviewed using the Edmonton Symptom Assessment System (ESAS) questionnaire, with 11 items describing cancer-related symptoms in visual analogue scale (VAS). Routine haematological samples were analysed at the time of interview. Both univariate and multivariate analyses were used to assess the independent predictors of fatigue. Out of the 10 symptoms recorded, fatigue was the single most frequent, reported by 91.3% of the patients, followed by pain (74.8%), sleeplessness (78.0%) and depression (74.2%). Anaemia was a significant determinant of fatigue (p=0.040)(OR=5.09; 95% CI 1.013-25.647). Out of the symptoms recorded, fatigue was significantly associated with depression (p=0.035), loss of appetite (p=0.016), anxiety (p=0.050), and sleeplessness (p=0.016). Total wellbeing was negatively associated with fatigue (OR=0.48, 95% CI 0.011-0.020)(p=0.0001). In multivariate analysis, anaemia was the most powerful independent predictor of fatigue, with OR=38.27 (95% CI 2.62-559.19)(p=0.008), followed by sleeplessness (OR=14.06 95% CI 1.44-137.02 p=0.023) and loss of appetite (OR=10.30 95% CI 1.04-101.10, p=0.045). Fatigue was unrelated to sex or age, or to the type of cancer, or the treatment category. Fatigue was common among cancer patients on palliative care. The single most powerful independent explanatory factor of fatigue was anaemia, implicating a need for interventional studies.*

Patients with advanced and progressing cancer have usually received multiple treatments and they suffer from cancer- or treatment-related symptoms. In the 1980s, the main

Correspondence to: Professor Eeva Salminen, MD, Ph.D., Department of Oncology and Radiotherapy, Turku University Hospital, Savitehtaankatu 1, FIN-20521 Turku, Finland. Tel: +358 23132817, Fax: +358 23336884, e-mail: eevsal@utu.fi

Key Words: Cancer patients, palliative care, fatigue, anaemia.

symptoms among these patients were nausea, vomiting and loss of hair. Only recently, has fatigue been recognised as a significant symptom among cancer patients (1, 2), and therapeutic interventions are emerging.

In cancer, fatigue occurs both as a result of the cancer and its treatment and it interferes with the patient's ability to perform physical and social activities. Criteria of cancer-related fatigue have been proposed by the International Classification of Diseases (ICD). By definition, fatigue is an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with functioning (3). Manifestations of fatigue have been studied in patients with breast cancer (4-6), gynaecological cancer (7-10) head and neck carcinomas (11) and more recently, in patients on hormonal treatment for prostate cancer (12). In practically all these studies, fatigue was disclosed to be a common symptom, with a multitude of causative factors related to cahexia, depression, medications, infections and hypogonadism (3, 13).

Anaemia is caused by a decrease in blood red cells, for whatever reason, and diagnosed as low levels of serum haemoglobin (Hb). According to the WHO criteria, anaemia is defined as Hb levels below 130 g/l for men and <120 g/l for women (14). Among cancer patients, the most common type of anaemia is normochromic and normocytic anaemia, which is indistinguishable from that seen in other chronic diseases. Anaemia is classified as mild, moderate or severe, but this distinction does not necessarily reflect the performance status of the patient. The latter depends on the adaptation, the rapidity of development of anaemia and the level of tissue oxygenation (15). Anaemia is a common consequence of cancer treatment (16). Importantly, however, it has been demonstrated that the quality of life (QoL) is improved, if anaemia is adequately corrected (17, 18).

The Edmonton Symptom Assessment Scale (ESAS) is a validated research tool which is routinely used in many clinics for the grading of subjective symptom intensity among cancer patients (19). ESAS was adopted for use when palliative care outpatient services were set up in our hospital in 2005. It was soon found to be particularly appropriate for Finnish patients due to its similarity to the 10-grade scoring system used by all schools in this country, making it easily accepted by the

patients. The fatigue scores as measured by using the ESAS fatigue subscale are consistent with those measured by the validated FACT-F (Functional Assessment of Cancer Therapy: Fatigue) instrument and other similar tools (20, 21).

This study was conducted in order to assess the prevalence of fatigue among breast and prostate cancer patients in comparison to other cancer patients and the role of Hb levels and other predictors of fatigue among these patients.

Patients and Methods

Patients. The material of the present study consisted of a series of 128 consecutive patients who were interviewed during a 4-month period (February-May, 2006) in the wards and outpatient palliative care facility of the Department of Oncology and Radiotherapy, Turku University Hospital. Patients aged over 18 years and able to communicate adequately on understanding of the concept of informed consent were enrolled in the study. The cohort included patients with breast (N=38) and prostate (N=20) cancer as well as those (N=70) with a variety of other carcinomas, including those of head and neck, gastrointestinal tract, brain tumours, mesothelioma and lung cancer and melanoma. Patients with lymphoma and testicular cancer were excluded due to their mostly curative treatment intent, as were the patients who were too weak to communicate sufficiently (minimum 30 minutes), or already receiving end-of-life care. The final cohort included 61 men and 67 women, with the mean age of 63.6 years (range 36-85). As to their treatment indications, 48.4% of the patients received palliative chemotherapy, 21.9% were treated with palliative radiotherapy and 29.7% were on palliative care without specific anticancer treatment.

Methods. Under the instructions of a doctor or a specialist nurse, all the patients filled in an ESAS-questionnaire. ESAS questionnaires have eleven items including 10 symptoms and the record of general wellbeing (1) as shown in Table I. ESAS is an independently validated tool (20) that allows simple bedside assessment of symptoms on a 0 (no symptom) to 10 (worst possible symptom) intensity scale. In the ESAS protocol, the 4 cut-off score is considered as an indicator of a need for therapeutic check-up and/or intervention for all the symptoms except for depression and anxiety, where the cut-off level of 2 is applied (22).

Routine blood tests were taken and analysed for the common haematological variables as well as for liver enzymes and creatinine, using the standard laboratory techniques. The cut-off values for anaemia used by our laboratory are: Hb <117 g/l (female) and Hb <134 g/l (male). We decided to use these as they have been validated for Finnish patients, although they are slightly lower or higher, respectively, than in the WHO definition (14).

The study was approved by the Ethical Committee of the Hospital District of South Western Finland and Turku University Hospital, and all the patients gave their written consent to participate in the study.

Statistical methods. All the statistical analyses were performed using the SPSS® (SPSS Inc., Chicago, Illinois, USA) and STATA (Stata Corp., College Station, Texas, USA) software packages (SPSS for Windows, version 14.01 and STATA/SE 9.2). Frequency tables were analyzed using the Chi-square test, with likelihood ratio (LR) or Fisher's exact test being used to assess the significance levels between the categorical variables. Odds ratios (OR) and their 95%

Table I. *Patient characteristics and ESAS variable distribution among 128 palliative cancer patients.*

Patients	N=128
Male	61
Female	67
Age (years)	64 (36-85)
Cancer	
Breast	38 (30%)
Prostate	20 (16%)
Other	70 (54%)
Treatment	
Chemotherapy	62 (48%)
Radiotherapy	28 (22%)
Other	38 (30%)
ESAS assessment: Mean (SD)	
Pain at rest	2.3 (2.4)
Pain at effort	3.0 (2.8)
Fatigue	4.0 (2.5)
Nausea	1.6 (2.4)
Depression	2.8 (2.5)
Anxiety	2.0 (2.3)
Dyspnoea	1.8 (2.3)
Loss of appetite	3.1 (3.3)
Constipation	2.9 (3.1)
Sleeplessness	2.6 (2.2)
Total well being	3.5 (2.3)

confidence intervals (95% CI) were calculated where appropriate, using the exact method. Differences in the means of continuous variables were analyzed using the non-parametric tests (Mann-Whitney, Kruskal-Wallis) or ANOVA (analysis of variance), after rigorous testing for the normal distribution by the Kolmogorov-Smirnov test. Multivariate logistic regression models were used to assess the independent predictors of the outcome measure (fatigue) using a stepwise forward and/or backward approach, with default values of entry (0.05) and removal (0.1). In all the tests, $p<0.05$ was regarded as statistically significant.

Results

The patient characteristics and information on symptom intensity as measured by ESAS are shown in Table I. Out of the 10 symptoms recorded, fatigue was the single most frequent, reported by 91.3% of the patents, followed by pain (74.8%), sleeplessness (78.0%) and depression (74.2%). Nausea was the least frequent, reported by 46.9% of the patients only. There was a significant difference in the score frequencies between the 10 symptoms ($p=0.0001$), the highest frequency (53.2%) of the high scores being confined to fatigue. In the subsequent analyses, the assessment of the determinants of fatigue among these patients was focused upon.

Table II lists the determinants of anaemia in univariate analysis. Anaemia was significantly ($p=0.0001$) more frequent among men (49/61, 80.3%) than in women (21/63, 33.3%). Anaemia was significantly ($p=0.0001$) related to cancer type, the prostate cancer patients showing the highest frequency

Table II. *Determinants of anaemia in univariate analysis*.

Variable	Anaemia*				OR (95% CI)	Significance
	Present		Absent			
Gender						
Men	49	80.3%	12	19.7%	8.16 (3.59-18.54)	*p*=0.0001
Women	21	33.3%	42	66.7%		
Age						
Below median	36	51.4%	34	48.6%	0.62 (0.30-1.28)	*p*=0.208
Above median	34	63.0%	20	37.0%		
Cancer type						
Breast	11	31.4%	24	68.6%		***p*=0.0001**
Prostate	17	85.0%	3	15.0%		
Other	42	60.9%	27	39.1%		
Treatment category						
Palliative chemotherapy	34	55.7%	27	44.3%		
Palliative radiotherapy	12	42.9%	16	57.1%		*p*=0.129
Advanced disease,						
No therapy	24	68.6%	11	21.4%		
Pain at rest						
Yes	49	57.6%	36	42.4%	1.16 (0.54-2.50)	*p*=0.692
No	21	53.8%	18	46.2%		
Pain at effort						
Yes	54	59.3%	37	40.7%	1.65 (0.73-3.72)	*p*=0.223
No	15	46.9%	17	53.1%		
Fatigue						
Yes	67	59.3%	46	40.7%	5.09 (1.01-25.64)	***p*=0.040**
No	2	22.2%	7	77.8%		
Nausea						
Yes	32	55.2%	26	44.8%	0.90 (0.44-1.84)	*p*=0.788
No	38	57.6%	28	42.4%		
Depression						
Yes	49	53.3%	43	46.7%	0.59 (0.25-1.37)	*p*=0.221
No	21	65.6%	11	34.4%		
Dyspnoea						
Yes	41	60.3%	27	39.7%	1.41 (0.69-2.88)	*p*=0.342
No	29	51.8%	27	48.2%		
Loss of appetite						
Yes	49	59.8%	33	40.2%	1.41 (0.66-3.00)	*p*=0.368
No	21	51.2%	20	48.8%		
Anxiety						
Yes	40	54.1%	34	45.9%	0.78 (0.37-1.62)	*p*=0.512
No	30	60.0%	20	40.0%		
Constipation						
Yes	43	56.6%	33	43.4%	1.01 (0.48-2.10)	*p*=0.971
No	27	56.3%	21	43.7%		
Sleeplessness						
Yes	51	53.1%	45	46.9%	0.56 (0.23-1.38)	*p*=0.206
No	18	66.7%	9	33.3%		
General well being						
Good	7	63.6%	4	36.4%	1.29 (0.35-4.69)	*p*=0.759
Impaired	62	57.4%	46	42.6%		

*Hb<134 in men and Hb<117 in women.

(85%) and the breast cancer patients the lowest frequency (31.4%). The treatment categories did not markedly deviate as to the frequency of anaemia. Out of the 11 symptoms recorded, fatigue was the only one to be significantly (*p*=0.040) associated with anaemia (OR=5.09; 95% CI 1.01-25.65). Anaemia was not significantly associated with patients' age (*p*=0.354), although most frequent (67.5%) among the 61-70-year age group (data not shown).

Table III. *Determinants of fatigue in univariate analysis.*

Variable	Fatigue*				OR (95% CI)	Significance
	Present		Absent			
Gender						
Male	57	95.0%	3	5.0%	2.62 (0.66-10.37)	p=0.212
Female	58	87.9%	8	12.1%		
Age						
Below median	63	88.7%	8	11.3%	0.45 (0.11-1.80)	p=0.346
Above median	52	94.5%	3	5.5%		
Cancer type						
Breast	34	91.9%	3	8.1%		p=0.913
Prostate	19	95.0%	1	5.0%		
Other	62	89.9%	7	10.1%		
Treatment category						
Palliative Chemotherapy	54	87.1%	8	12.9%		
Palliative Radiotherapy	27	100.0%	0	00.0%		p=0.125
Advanced disease, No therapy	34	91.9%	3	8.1%		
Anaemia						
Yes	67	97.1%	2	40.7%	5.09 (1.01-25.64)	**p=0.040**
No	46	86.8%	7	13.2%		
Pain at rest						
Yes	80	93.0%	6	7.0%	1.90 (0.54-6.65)	p=0.324
No	35	87.5%	5	12.5%		
Pain at effort						
Yes	87	93.5%	6	6.5%	2.68 (0.75-9.49)	p=0.147
No	27	84.4%	5	15.6%		
Nausea						
Yes	57	96.6%	2	3.4%	4.42 (0.91-21.36)	p=0.060
No	58	86.6%	9	13.4%		
Depression						
Yes	88	94.6%	5	5.4%	3.91 (1.10-13.82)	**p=0.035**
No	27	81.8%	6	18.2%		
Dyspnoea						
Yes	64	95.5%	3	4.5%	3.34 (0.84-13.26)	p=0.112
No	51	86.4%	8	13.6%		
Loss of appetite						
Yes	78	96.3%	3	3.7%	5.77 (1.44-23.06)	**p=0.016**
No	36	81.8%	8	18.2%		
Anxiety						
Yes	71	95.9%	3	4.1%	4.30 (1.08-17.09)	**p=0.050**
No	44	84.6%	8	15.4%		
Constipation						
Yes	73	93.6%	5	6.4%	2.08 (0.60-7.25)	p=0.331
No	42	87.5%	6	12.5%		
Sleeplessness						
Yes	92	94.8%	5	5.2%	5.01 (1.40-17.95)	**p=0.016**
No	22	78.6%	6	21.4%		
General well being						
Good	6	50.0%	6	50.0%	0.48 (0.01-0.20)	**p=0.0001**
Impaired	104	95.4%	5	4.6%		

*Fatigue present or absent (scores 1-10 *vs*. score 0).

The determinants of fatigue in univariate analysis are listed in Table III. Fatigue was unrelated to sex or age, or to the type of cancer or the treatment category. Anaemia was a significant determinant of fatigue (p=0.040). Out of the symptoms recorded, fatigue was significantly associated with depression (p=0.035), loss of appetite (p=0.016), anxiety

Table IV. *Determinants of fatigue in multivariate analysis.*

Covariates	Crude OR (95% CI)	Significance	*Adjusted OR (95% C)	Significance
Age[1]	0.45 (0.11-1.80)	*p*=0.346	0.70 (0.09-5.21)	*p*=0.731
Anaemia[2]	5.09 (1.01-25.64)	*p*=0.040	38.27 (2.62-559.19)	***p*=0.008**
Depression	3.91 (1.10-13.82)	*p*=0.035	11.03 (0.77-158.10)	*p*=0.077
Loss of appetite	5.77 (1.44-23.06)	*p*=0.016	10.30 (1.04-101.10)	***p*=0.045**
Anxiety	4.30 (1.08-17.09)	*p*=0.050	0.17 (0.01-2.96)	*p*=0.227
Sleeplessness	5.01 (1.40-17.95)	*p*=0.016	14.06 (1.44-137.02)	***p*=0.023**
Cancer type		*p*=0.913		*p*=0.310
Other			Reference	
Breast			4.60 (0.15-142.12)	*p*=0.383
Prostate			5.48 (0.61-48.08)	*p*=0.126
Treatment category		*p*=0.125		*p*=0.600
Palliative				
Chemotherapy			Reference	
Palliative				
Radiotherapy			0.00 (0.00-)	*p*=0.998
Advanced disease			0.33 (0.041-2.78)	*p*=0.312

*Adjusted for all significant predictors in univariate analysis; [1]below and above median; [2]Hb<134 in men and Hb<117 in women.

(*p*=0.050), and sleeplessness (*p*=0.016). Not unexpectedly, reporting good wellbeing was negatively associated with fatigue (OR=0.48, 95% CI 0.01-0.02) (*p*=0.0001).

Table IV summarises the results of the multivariate logistic regression analysis for the independent determinants of fatigue. All the significant predictors in the univariate analysis (Table II) as well as age, type of cancer, and treatment category were entered as covariates in the regression model. Only three of the covariates were significant independent predictors of fatigue: anaemia, loss of appetite and sleeplessness, while the others lost their significance (*i.e.* were confounded) in the final multivariate model. Anaemia was by far the most powerful of these independent predictors, with OR=38.27 (95% CI 2.62-559.19) (*p*=0.008), followed by sleeplessness (OR=14.06, 95% CI 1.44-137.02, *p*=0.023) and loss of appetite (OR=10.30, 95% CI 1.04-101.10, *p*=0.045).

Discussion

In this study, we showed that the proportion of the cancer patients reporting fatigue was high, and fatigue could be assessed using ESAS because it is a subjective condition. Furthermore, anaemia was shown to be the most powerful independent determinant of fatigue among the cancer patients treated with palliative intention. The results provided further insights into the significant association between these two and other symptoms thus substantiating the reports of Noergaard Munch *et al*. (23) and Manusco *et al*. (24). In addition to anaemia, sleeplessness and loss of appetite were independent predictors of fatigue among these patients. This finding should have practical implications, warranting

intervention studies to overcome this common symptom when palliative patients are receiving chemotherapy or radiotherapy, and also offering possibilities for practitioners to improve the QoL of these patients.

The Hb level was an independent determinant of fatigue in the current study, in alignment with two other recent reports (10, 24). In two previous retrospective studies, normal Hb levels improved the prognosis, irrespective of whether these were natural or corrected with blood transfusions (7, 8). However, other studies have failed to show such a close association between anaemia and fatigue. Most likely, these different observations are related to differences in the study cohorts interviewed: patients with less advanced disease seem to show a stronger association between fatigue and anaemia than those on palliative care for advanced disease (23).

As a part of our ongoing systematic survey of different symptoms reported by cancer patients on palliative treatment, in the present study, we focused on fatigue, which proved to be the single most frequent symptom. In the present cohort, the single most important independent predictor of fatigue proved to be anaemia, followed by sleeplessness and loss of appetite. All these factors are important components of QoL and the association between anaemia, QoL functional capacity, the presence of co-morbidities and depression in elderly patients has been reported (24, 25). Anaemia seems to be a common finding particularly among elderly cancer patients (26). In the present study, however, the age of the patients was not directly associated with anaemia and fatigue in either women or men.

There was a higher prevalence of anaemia among men in the current study, which is explained by the high number of prostate cancer patients with advanced disease, treated with

androgen deprivation or castration. Among prostate cancer patients, increased fatigue has been recorded especially among those receiving hormonal treatment and having low levels of serum haemoglobin (Hb) (12). The increased use of androgen deprivation in the adjuvant setting is a significant factor increasing the prevalence of anaemia and fatigue among prostate cancer patients through bone marrow depression (12). Tools such as ESAS can serve the clinician by providing a more comprehensive view of the patient's problems. When completed while waiting to see the doctor, the use of ESAS forms does not necessarily increase the time needed to respond to the patient's needs.

The interrelations between the different symptoms in cancer patients have been studied to some extend before. Recently, a correlation between fatigue and depression has been indicated in a few studies (6, 23). Similarly, the connection between the most common symptoms, pain, fatigue, sleeplessness and depression is easily comprehensible (27). Indeed, pain and depression are closely linked. For instance, a third of breast cancer survivors indicated increased fatigue, which was reported to be associated with significantly high levels of depression, pain and sleep disturbances (17) and earlier chemotherapy. These were the most common symptoms reported by the patients in the present study as well.

There is no doubt that psychological syndromes may contribute to the feeling of fatigue. However, these are not easy to discover and even more difficult to adequately cope with. Importantly, the present study showed also a close and significant association between fatigue and Hb levels. Self-evidently, the latter can be more easily corrected than the distress due to psychological reasons. There is some evidence to suggest that different explanatory factors (co-variates) may be significant determinants of fatigue in different patients, for example among breast cancer patients receiving adjuvant radiotherapy, no correlation was established between fatigue and Hb levels (4). In a recent survey with a study design comparable to that of the present study, the authors used the Spearman correlation test and failed to demonstrate a significant correlation between fatigue and anaemia in their cohort of 177 patients (23). However, they reported a closer correlation between fatigue and anaemia among the patients with less advanced disease, as compared with those at the palliative unit. The patients in the present cohort had less advanced disease, 65% receiving either palliative chemotherapy or radiotherapy. In such patients, the treatment of anaemia may also improve the therapeutic effect, because tissue hypoxia decreases the sensitivity to cancer-specific treatments. When the present data were tested using the same approach (Spearman rank correlation), a significant negative correlation between Hb values and fatigue was disclosed (r=−295; p=0.001). If the WHO criteria for anaemia had been used in the present study, this association would have been even stronger.

Studies of symptom assessment in palliative cancer care have been criticized due to their possible selection bias, small sample size and high rate of non-response. We believe that the present survey was devoid of most of those potential biases. In the present setting, consecutive patients were met at the oncology ward by the doctor (ES) and/or the nurse (AL), and instructed how to complete the ESAS forms. The response rate in the present cohort was very high, only few of the 128 patients failing to respond to individual items requested. Furthermore, the results were consistent with the data reported in other studies using the ESAS protocol (21-23). Significant differences in the ratings of symptoms between the physicians and the patients have been observed previously (28-30). If not carefully considered, this can lead to failure of the physicians to respond to the patient's expression of fatigue. The ESAS protocol provides relatively simple tools to improve the awareness of a patient's symptoms in clinical practice.

Undoubtedly, the demonstration of anaemia as the single most powerful independent determinant of fatigue in multivariate analysis has important practical implications for cancer patients under palliative treatments. Understanding the association between Hb and fatigue elucidates more completely the components of patient QoL and recognition of this fact should help in improving the patient's general wellbeing. In a large retrospective analysis of over 4.000 patients, Crawford and colleagues demonstrated a direct relationship between increased Hb levels and QoL improvement (18). QoL has significantly improved when anaemia has been corrected both in patients with chemotherapy-induced anaemia and in those with anaemia due to chronic disease (14). For breast cancer, a recent consensus on medical treatment recommended that symptomatic anaemia (Hb below 11 g/dl) should be diagnosed, investigated and corrected (31). Over-correction is not recommended, however, because it may have a negative impact on the outcome (11). The optimal level appears to be 120-130 g/l, shown to be the most beneficial in a recent meta-analysis (32). Given the impact of fatigue on QoL, we feel that treatment options should be routinely considered in the palliative care of cancer patients.

In conclusion, fatigue is common among patients treated with palliative intent. Importantly, anaemia is the single most powerful independent determinant of fatigue which should have important practical implications, warranting intervention studies to overcome this common symptom, and offering possibilities to significantly improve the quality of life among these patients.

Acknowledgements

References

1 Bruera E, Kuehn N, Miller MJ, Selmser P and Macmillan K: The Edmonton Symptom Assessment System (ESAS). A simple method for assessment of palliative care patients. J Palliat Care *7*: 6-9, 1991.

2 Loge JH: Unpacking fatigue. Eur J Palliat Care *10*: 14-20, 2003.

3 NCCN Cancer–Related Fatigue Panel: National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Cancer-Related Fatigue, version 2, pp. 1-45, 2005.

4 Geinitz H, Zimmermann FB, Stoll P *et al*: Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. Int J Rad Oncol Biol Phys *51*: 691-698, 2001.

5 Servaes P, Verhagen CA and Bleijenberg C: Relations between fatigue, neuropsychological functioning and physical activity after treatment for breast cancer: daily self report and objective behaviour. Cancer *95*: 2017-2026, 2002.

6 De Jong N, Candel MJ, Schouten HC, Abu-Saad HH and Courtens AM: Course of mental fatigue and motivation in breast cancer patients receiving adjuvant chemotherapy. Ann Oncol *16*: 372-382, 2005.

7 Grogan M, Thomas GM, Melamed I *et al*: The importance of haemoglobin levels during radiotherapy for carcinoma of the cervix. Cancer *86*: 1528-1536, 1999.

8 Kapp KS, Poschauko J, Geyer E *et al*: Evaluation of the effect of routine packed red blood cell transfusion in anemic cervix cancer patients treated with radical radiotherapy. Int J Radiat Oncol Biol Phys *54*: 56-58, 2002.

9 Munstedt K, Johnson P, Bohlmann MK *et al*: Adjuvant radiotherapy in carcinomas of the uterine cervix: the prognostic value of haemoglobin levels. Int J Gynecol Cancer *15*: 285-291, 2005.

10 Di Maio P, Pisang C, Tambaro R *et al*: The prognostic role of pre-chemotherapy hemoglobin level in patients with ovarian cancer. Front Bioscience *11*: 1585-1590, 2006.

11 Henke M, Sindlinger F, Ikenberg H *et al*: Erythropoietin to treat head and neck cancer patients with anemia undergoing radiotherapy: randomized, double blind placebo controlled trial. Lancet *362*: 1255-1260, 2003.

12 Joly F, Alibhai SM, Galica J, Park A, Yi QL, Wagner L and Tannock IF: Impact of androgen deprivation therapy on physical and cognitive function, as well as quality of life of patients with non-metastatic prostate cancer. J Urol *176*: 2443-2447, 2006.

13 Stone P, Hardy J, Broadley K, Tookman AJ, Kurowska A and A'Hern R: Fatigue in advanced cancer; a prospective controlled cross-sectional study. Br J Cancer *79*: 1479-1486, 1999.

14 Bokemeyer C, Aapro MS, Courdi A *et al*: EORTC guidelines for the use of erythropoietic proteins in anemic patients with cancer. Eur J Cancer *40*: 2201-2216, 2004.

15 Caro JJ, Salas M, Ward A and Goss G: Anemia as independent prognostic factor for survival in patients with cancer: a systematic, quantitative review. Cancer *91*: 2214-2221, 2001.

16 Groopman JE and Itri LM: Chemotherapy induced anemia in adults. Incidence and treatment. J Natl Cancer Inst *91*: 1616-1634, 1999.

17 Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE and Belin TR: Fatigue in breast cancer survivors: occurrence, correlates and impact on quality of life. J Clin Oncol *18*: 743-753, 2000.

18 Crawford J, Cella D, Cleeland CS *et al*: Relationship between changes in haemoglobin and quality of life during chemotherapy in anemic cancer patients receiving e-poetin alpha therapy. Cancer *95*: 888-895, 2002.

19 Dudgeon DJ, Harlos M and Clinch JJ: The Edmonton Symptom Assessment Scale (ESAS) as an audit tool. J Palliat Care *15*: 14-19, 1999.

20 Chang VT, Hwang SS and Feuerman M: Validation of the Edmonton Symptom Assessment scale. Cancer *88*: 2164-2171, 2000.

21 Bruera E, Neumann C, Brenneis C and Quan H: Frequency of symptom distress and poor prognostic indicators in palliative care patients admitted to a tertiary palliative care unit, hospices and acute care hospitals. J Palliat Care *16*: 16-21, 2000

22 Vignaroli E, Pace EA, Willey J, Palmer JL, Zhang T and Bruera E: The Edmonton Symptom Assessment System as a screening tool for depression and anxiety. J Pall Med *2*: 296-303, 2006.

23 Noergaard Munch T, Zhang T, Willey J, Palmer JL and Bruera E: The association between anemia and fatigue in patients with advanced cancer receiving palliative care. J Palliat Med *8*: 1144-1149, 2005.

24 Manusco A, Migliorino M, De Santis S, Saponiero A and De Mannis F: Correlation between anemia and functional/cognitive capacity in elderly lung cancer patients treated with chemotherapy. Ann Oncol *17*: 146-150, 2006.

25 Salminen E, Portin R, Koskinen A, Helenius H and Nurmi M: Association of cognitive function and estrogen decline during androgen deprivation in prostate cancer patients. Br J Cancer *89*: 971-976, 2003.

26 Ania BJ, Suman VJ, Fairbanks VF, Rademacher DM and Melton LJ: Incidence of anemia in older people, an epidemiologic study of a well-defined patient population. J Am Geriatr *45*: 825-831, 1997.

27 Barkwell DP: Ascribed meaning: a critical factor in coping and pain attenuation in patients with cancer-related pain. J Palliat Care *7*: 5-14, 1991.

28 Anderson KO, Mendeza TR, Valero V *et al*: Minority cancer patients and their providers: Pain management attitudes and practice. Cancer *88*: 1929-1938, 2000.

29 Cascinu S, Giordani P, Agostinelli R *et al*: Pain and its treatment in hospitalised patients with metastatic cancer. Support Care Cancer *11*: 587-592, 2003.

30 Salminen E, Clemens KE, Syrjänen K and Salmenoja H: Needs of developing the skills of palliative care at the oncology ward: An audit of symptoms among 203 consecutive cancer patients in Finland. Support Care Cancer *16*: 3-8, 2008.

31 Basilja S, Bonneterre J, Bursten H. *et al*: Second consensus on medical treatment of metastatic breast cancer. Ann Oncol *18*: 215-225, 2007.

31 Bohlius JF, Langensiepen S, Schwarzwer G *et al*: Does erythropoietin improve survival in the treatment of patients with malignant diseases? Results of comprehensive meta-analysis. Blood 102 suppl, abstract 709, 2003.

32 Curt GA, Breitbart W, Cella D *et al*: Impact of cancer-related fatigue on the lives of the patients: new findings from the Fatigue Coalition. Oncologist *5*: 353-360, 2000.