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ORIGINAL ARTICLE

Cancer-related fatigue: clinical practice versus practice guidelines

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Abstract
Purpose This study investigated adherence to treatment guidelines on cancer-related anaemia and fatigue (CRA/CRF) and factors influencing the choice of intervention.
Methods In this prospective, observational study, 136 cancer patients being treated with chemotherapy in a large community hospital completed a questionnaire at consecutive outpatient visits assessing fatigue (the Functional Assessment of Chronic Illness Therapy—Fatigue) and fatigue-related counselling and advice received. Data on administration of chemotherapy and use of epoetin or blood transfusions were abstracted from the medical records.
Results Fifty-three percent of patients with severe anaemia (Hb<10 g/dl) and 6% of patients with less severe anaemia (Hb levels 10–12 g/dl) received treatment (epoetin and/or blood transfusions). Half of the patients with less severe anaemia reported clinically relevant levels of fatigue. More than 50% of all patients received fatigue-related counselling, primarily at the start of chemotherapy. Most counselling was directed at energy conservation. Fatigue was not associated significantly with the use of epoetin or blood transfusion. Patients receiving palliative treatment (17%), male patients (16%) and patients with a low Hb level (<6.2 g/dl, 38%) were treated significantly more often with epoetin.
Conclusions In daily clinical practice, guidelines concerning the use of epoetin or blood transfusion in severe CRA are adhered to in about half of the cases. In patients with less severe anaemia, the level of fatigue did not play a significant role in the use of epoetin. According to current guidelines, counselling on CRF should be directed primarily at activity enhancement. However, only a minority of patients receive such counselling.

Keywords Fatigue · Guidelines · Anaemia · Counselling · Chemotherapy · Quality of life

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Introduction

Fatigue is a very common symptom among patients with cancer [1]. When persistent, fatigue can seriously inhibit patients' ability to participate fully in the roles and activities that make life meaningful [2, 3]. Cancer-related fatigue is defined by the NCCN as a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [1].

The aetiology of cancer-related fatigue (CRF) is multifactorial and its treatment multimodal, including medical,

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behavioural and psychological interventions. Factors contributing to CRF that are potentially amenable to treatment include pain, emotional distress, sleep disturbance, nutrition, activity level, comorbidity and anaemia [1]. Fatigue is associated with a diminished quality of life [3] and may be treated with counselling as well as pharmacological interventions, when applicable.

Counselling approaches to the treatment of CRF include education, counselling and behavioural interventions on activity enhancement, nutrition and sleep [1, 4]. Similar interventions are recommended in the Dutch guidelines on counselling for CRF [5]. Of these interventions during active cancer treatment, activity enhancement has been shown to result in a reduction in fatigue levels of 40–50% [6, 7].

However, when CRF is caused by cancer-related anaemia (CRA), pharmalogical interventions are indicated. The most widely investigated pharmacological intervention is the administration of epoetin. In 2002, the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) developed an evidence-based clinical practice guideline for the use of epoetin in patients with cancer [8]. The guideline was updated in 2007 [9]. The use of epoetin is recommended as an option for patients with chemotherapy-associated anaemia with a haemoglobin level of less than 10 g/dl (6.2 mmol/l). Use of epoetin for patients with less severe anaemia (haemoglobin < 12 g/dl (<7.4 mmol/l) but not below 10 g/dl) should be determined by clinical circumstances. In the 2007 update, substantially reduced exercise capacity, lack of energy or limited ability to carry out activities of daily living were included as clinical circumstances to be taken into consideration when deciding on the use of epoetin in patients with less severe anaemia.

Despite the growing body of evidence on the impact of fatigue on cancer patients' health-related quality of life (HRQL), it remains under-reported, under-diagnosed and under-treated. For example, in a survey among 419 cancer patients, 78% reported experiencing fatigue, but only 50% discussed it with their oncologist, and only 27% received any counselling or treatment [10]. In another study, only 14% of patients reporting moderate or severe fatigue received treatment or counselling [11]. In a large European survey on the pharmacological treatment of CRA, 39% of anaemic patients received epoetin, transfusion or iron supplement [12]. In an observational study among 15 oncologists and 36 patients, most discussions of and counselling for fatigue were found to be very general and imprecise [13].

To our knowledge, no study has yet investigated the association between clinical signs and symptoms of fatigue and its treatment in daily clinical practice. The current—observational—study was undertaken to (1) document treatment for CRF in daily clinical practice, (2) determine the extent to which clinical practice reflects current evidence-based practice guidelines for CRF and (3) identify factors influencing choice of treatment and counselling.

Methods

Study site and subjects

The study was conducted at the outpatient oncology clinic of the Medical Center Alkmaar, a general community teaching hospital located north of Amsterdam. On average, 1,700 newly diagnosed cancer patients are treated annually in this hospital. Eighty percent of cancer patients in the Netherlands are treated in general community hospitals [14].

The study sample was composed of a consecutive series of cancer patients starting chemotherapy treatment. Patients were excluded if they lacked basic proficiency in Dutch or were younger than 18 years of age. Eligible patients were given verbal and written information about the study prior to obtaining their informed consent. The institutional review board of the hospital approved the study.

The management of CRA and CRF was studied without the medical and nursing staff being informed of the purpose of the study. The nurses had been trained previously in the use of the Dutch guidelines for counselling on cancer-related fatigue [5] (see Table 1). These guidelines parallel the international guidelines of the Oncology Nursing Society [4].

Study design and procedures

This was a prospective, observational study. Patients were asked to participate in the study before their initial outpatient chemotherapy visit. After providing informed consent, they were followed up during consecutive outpatient visits, with a maximum of five visits.

Study measures

Patients' sociodemographic and clinical characteristics

At the time of the initial outpatient visit, patients' age and gender were recorded, and clinical information, including WHO performance status, tumour type, prior surgical and/or radiotherapy treatment, chemotherapy treatment intent (i.e. curative, (neo)adjuvant or palliative) and chemotherapy schedule were extracted from the medical records.

Table 1 The Dutch nursing guidelines on fatigue

The guideline consist of the following chapters
Diagnosis
Prognosis and proposed results
Interventions
Evaluation
All interventions are based on McCloskey and Bulechek [30]. The interventions described are in addition to general information on fatigue:
Energy regulation (balancing activities and rest to ensure that patients can perform the activities they wish to carry out)
Improving sleep (the rationale being that sleep disturbances may cause fatigue and may lead to inactivity)
Appropriate nutrition (to avoid malnutrition, weight loss and dehydration, which can cause fatigue)
Improving physical activity
Restorative therapy (e.g. reducing conflicts, stress, worries, etc., through recreation and relaxation)

Haemoglobin level

Haemoglobin level was assessed before each chemotherapy cycle. Patients were divided into three groups according to their Hb level: <10 g/dl (severe anaemia), 10–12 g/dl (less severe anaemia) and >12 g/dl (no anaemia). These three categories reflect the ASCO guidelines on the use of epoetin in patients with cancer.

Fatigue

Before each study visit, patients were asked to complete a standardised fatigue questionnaire, the Functional Assessment of Chronic Illness Therapy—Fatigue Scale (FACIT-F Scale) [15], via a touch screen computer. The FACIT-F scale is a 13-item questionnaire assessing fatigue and its impact on daily activities and function during the previous 7-day period. A FACIT-F score of 30 is considered to be a threshold for distinguishing between fatigued and non-fatigued patients [16].

In this outpatient clinic, routine assessment and presentation of patients' HRQL via touch screen technology had already been implemented, and the fatigue assessment was embedded in that assessment procedure. However, results of the fatigue questionnaire were not presented to either the patients, the medical oncologist or to the oncology nurses [17].

Treatment and counselling on fatigue

Information on blood transfusions and prescription of epoetin was obtained from the medical records. Following each cycle of chemotherapy, patients were asked to report any counselling or advice that they had received from the nursing or medical staff related to fatigue. The fatigue-related counselling was grouped into six categories according to the Dutch guidelines (see Table 1), including (1) general information and education, (2) energy regulation, (3) sleep, (4) nutrition, (5) exercise and (6) relaxation.

Statistical analysis

To evaluate the adherence to clinical practice guidelines on CRA (i.e. the use of epoetin and blood transfusion), patients were divided into three groups according to their haemoglobin level: severely anaemic patients with Hb levels <10 g/dl, less severely anaemic patients with Hb levels between 10 and 12 g/dl and non-anaemic patients with Hb level >12 g/dl. Adherence was established by comparing the actual pharmacological treatment of the three groups to the guidelines. Severely anaemic patients were further divided into two groups based on the duration of the anaemia (during one chemotherapy cycle only versus during more than one chemotherapy cycle). Differences in the pharmacological treatment of patients with long- versus short-term anaemia were tested with Fisher's exact test.

Logistic regression analysis was performed with epoetin use or blood transfusion as the dependent variables and sex, treatment intent (i.e. adjuvant/curative versus palliative), haemoglobin level, level of fatigue and age as independent variables.

For the analysis of counselling, multinomial logistic regression analysis was performed, with type of counselling (energy conservation, physical activity, both types of counselling or neither type of counselling) as the dependent variable and age, sex, treatment intent (i.e. adjuvant/curative versus palliative), haemoglobin level and level of fatigue as independent variables. This regression analysis was limited to these types of counselling because less than 5% of patients received counselling on sleep therapy, nutrition and/or restorative therapy.

Table 2 Patient characteristics

		n (%)
Gender	Female	84 (61.8)
	Male	52 (38.2)
Age (range)		62 (40–87)
Type of chemotherapy	Curative/adjuvant	57 (41.9)
	Palliative	69 (50.7)
	Neo-adjuvant	10 (7.4)
Radiotherapy		39 (28.7)
	Before chemotherapy	19 (48.7)
	During chemotherapy	18 (46.2)
	After chemotherapy	2 (5.1)
Surgery		63 (46.3)
Primary cancer	Breast	52 (38.2)
	Lung	29 (21.3)
	Colorectal	33 (24.3)
	Urogenital	4 (2.9)
	Gynaecological	5 (3.7)
	Lymphoma	8 (5.8)
	Other	5 (3.7)
Number of chemotherapy cycles	1	14 (10.3)
	2	13 (9.6)
	3	9 (6.6)
	4	22 (16.2)
	5 or more	78 (57.4)

Multilevel logistic regression analysis, with counselling (yes versus no) as the dependent variable and age, sex, treatment intent (i.e. adjuvant/curative versus palliative), haemoglobin level and level of fatigue as independent variables was performed to investigate the temporal pattern of advice during the course of treatment.

Assuming a 20% to 25% difference between the proportion of patients receiving a given treatment as a function of Hb level, with alpha set at 5% and power at 80%, 128 patients were required [18].

Results

Patient and nurses recruitment and sample description

Between January 2006 and November 2006, 140 patients were invited to participate in the study, of whom 136 agreed (97% response rate).

Table 2 presents the patients' sociodemographic and clinical characteristics. The median age of the patients was 62 years, and 62% was female. More than half of the patients were receiving treatment for breast cancer. Approximately half of the patients were receiving palliative treatment.

Treatment for CRA

Table 3 presents results on the treatment of anaemia in relation to patients' Hb and fatigue levels. Twenty-six of the 136 patients (19.1%) had an Hb<10 g/dl, indicative of severe anaemia. The ASCO guidelines recommend treating these patients with epoetin. Blood transfusion is also a treatment option. Fourteen (54%) of these patients actually received treatment with epoetin and/or blood transfusion. However, when anaemia was not related to chemotherapy, patients were treated conforming to standard hospital procedures. These other causes were not further investigated in the present study.

Seventy-two patients (52.9%) had an Hb value between 10 and 12 g/dl. According to the prevailing treatment guidelines, use of epoetin and/or blood transfusions for patients with less severe anaemia should be determined on the basis of clinical observation of symptoms. Of these 72 patients, only four (5.5%) received epoetin and/or a blood transfusion. However, half of these 72 patients with less severe anaemia reported clinically relevant levels of fatigue (i.e. FACIT-F scores of 30 or less).

Finally, 38 patients (27.9%) had Hb levels above 12 g/dl. None of these patients received treatment with epoetin, which is in accordance with the guidelines. However, one patient received a blood transfusion.

Table 3 Pharmacological interventions for fatigue in relation to haemoglobin level as defined by the ASCO guidelines and level of fatigue

Pharmacological intervention	Hb<10 g/dl[a] *n*=26	Hb 10–12 g/dl *n*=72		Hb>12 g/dl *n*=38
	n	FACIT-F<30[b] *n*=36 *n*	FACIT-F>30 *n*=36 *n*	*n*
Epoetin	6	1	1	0
Blood transfusion	5	0	1	1
Epoetin and blood transfusion	3	0	1	0
No treatment	12	35	33	37

[a] Hb levels corresponding to ASCO guidelines on use of epoetin

[b] A score of 30 on the FACIT-F scale is the threshold for distinguishing between fatigued and non-fatigued patients

Table 4 Pharmacological interventions for patients with a Hb level <10 g/dl during one versus more than one chemotherapy cycle

Pharmacological treatment (epoetin and/or blood transfusion)	Hb level <10 g/dl during more than one chemotherapy treatment cycle	
	Yes (n=7)	No (n=19)
Yes (n=14)	3	11
No (n=12)	4	8

p=0.67 (Fisher exact test)

Table 4 presents the data on the association between duration of anaemia and treatment. Nineteen of the 26 severely anaemic patients experienced an Hb of <10 g/dl on only one occasion, of whom 11 (58%) received treatment (epoetin and/or blood transfusion). Seven of the 26 severely anaemic patients experienced an Hb<10 g/dl during more than one treatment cycle, of whom three (43%) received treatment. Thus, the duration of the anaemia was not a significant factor in the decision to use epoetin or blood transfusions (p=0.67).

Table 5 presents the results of the analysis of predictors of pharmacological treatment. Seventeen percent of the patients receiving palliative treatment versus 2% of those receiving adjuvant/curative treatment were treated with epoetin (p=0.01, OR=45.8). Sixteen percent of the male patients versus 5% of the female patients were treated with epoetin (p=0.03, OR=0.09). As expected, significantly more patients with a lower Hb level (38%) were treated with epoetin (p<0.001, OR=0.07) and blood transfusions (p=0.001, OR=0.14) than patients with a higher Hb level (3%; p<0.001). Level of fatigue was not associated significantly with the use of epoetin or blood transfusion.

Counselling for fatigue

Table 6 presents the results pertaining to counselling for cancer-related fatigue. Sixty-three percent of patients received counselling for CRF. More than half of the patients (n=75; 55%) received counselling on energy conservation, 24 patients (18%) received counselling on physical activity and less than 5% of patients received counselling on sleep therapy, nutrition and/or restorative therapy. Multinomial logistic regression analyses indicated that patients with a higher FACIT-F score (i.e. less fatigued) were more likely to receive counselling on energy conservation (p=0.002, OR 1.07). Hb level, age, treatment intent and sex were not associated significantly with the type of counselling.

Approximately half of the patients received counselling on CRF during the first cycle of chemotherapy. Across

Table 5 Logistic regression analysis on the use of epoetin and/or blood transfusion

		% Patients receiving epoetin	OR	CI	p value[a]	% Patients receiving blood transfusion	OR	CI	p value[a]
Age	<60 (n=61)	11	0.9	0.9–1.0	0.2	3	1.0	1.0–1.1	0.4
	>60 (n=70)	7				13			
Sex	Male (n=50)	16	0.09	0.01–0.82	0.03	16	0.23	0.04–1.2	0.09
	Female (n=81)	5				4			
Treatment intent	Adjuvant/ curative (n=66)	2	45.8	2.3–910	0.01	6	0.55	0.1–3.2	0.5
	Palliative (n=65)	17				11			
Hb level[b]	<10 g/dl (n=24)	38	0.07	0.02–0.3	<0.001	33	0.14	0.04–0.4	0.001
	>10 g/dl (n=107)	3				3			
FACIT-F[b]	<30 (n=67)	6	1.1	1.0–1.2	0.06	9	1.0	0.9–1.1	0.9
	>30 (n=64)	13				8			

[a] p value based on logistic regression analysis with the binary variables sex and treatment intent and the continuous variables age, Hb level and FACIT-F as independent variables

[b] Lowest level during all treatment courses

Table 6 Number of patients receiving counselling on cancer-related fatigue as a function of self-reported fatigue levels

Counselling	FACIT-F<30[a] (*n*=35) *n* (%)	FACIT-F>30 (*n*=101) *n* (%)	*p* value	Total (*n*=136) *n* (%)
Energy conservation	9 (26)	66 (65)	<0.01[b]	75 (55)
Sleep	0 (0)	4 (4)	0.57[c]	4 (3)
Nutrition	1 (3)	1 (1)	0.45[c]	2 (2)
Physical activity	6 (17)	18 (18)	0.93[b]	24 (18)
Restorative therapy	0 (0)	0 (0)	–	0 (0)

[a] Score at first visit, a score of 30 on the FACIT-F scale is the threshold for distinguishing between fatigued and non-fatigued patients

[b] Chi-square statistic

[c] Fisher's exact test

cycles, 63% of patients received such counselling. Multilevel logistic regression analysis confirmed that patients were counselled significantly more often at the beginning of the treatment ($p<0.05$), as compared to during other treatment cycles. This was not influenced by patient or treatment characteristics, including Hb levels (data not shown).

Discussion

In this observational study, we found that only 53% of patients with severe CRA (Hb<10 g/dl) and 6% of patients with less severe CRA (Hb levels 10–12 g/dl) received treatment with epoetin and/or blood transfusions. In addition, approximately 50% of patients with less severe anaemia experienced fatigue and thus, according to current practice guidelines, should have been considered for treatment. More than 50% of the patients received specific fatigue-related counselling. Most counselling was directed at energy conservation.

In 2002 and 2007, the ASCO and the ASH published evidence-based guidelines on the use of epoetin and blood transfusion in patients with cancer [8, 9]. In our study, only a minority of patients actually received treatment with epoetin, although approximately half of the patients could have been considered for such treatment based on their Hb level alone or in combination with their self-reported fatigue levels. While the ASCO guidelines mention the relevance of clinical circumstances in determining the appropriateness of medical intervention for fatigue, they do not provide explicit criteria in this regard. The European Cancer Anaemia Survey (ECAS) of more than 15,000 cancer patients found that more than 60% of anaemic patients are not treated with epoetin [12].

In our study, several factors may have played a role in the limited adherence to guidelines on the use of epoetin. First, safety issues may have influenced treatment decisions. Several recent studies have reported that the use of epoetin in cancer patients can have a negative impact on survival [19–21]. These findings triggered a review by the US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee and resulted in the FDA updating the product labelling of epoetin. It should be noted, however, that the risks for higher mortality and/or shortened time to tumour progression were demonstrated in studies where epoetins were dosed with the intent to achieve Hb values greater than or equal to 12 g/dl [22]. The risk of shortened survival and tumour progression have not been demonstrated when epoetins are dosed to reach a haemoglobin value of <12 g/dl. Nevertheless, the place of epoetin in the treatment of CRA and CRF remains the subject of continued discussion, particularly in patients with advanced cancer receiving palliative care [23].

A second factor possibly related to the limited use of epoetins is the failure of health care providers to recognise clinically relevant levels of fatigue. Again, although practice guidelines indicate that clinical circumstances should contribute to decisions regarding the use of epoetin or blood transfusions, no specific guidance is provided as to how such clinical circumstances, including assessment of fatigue, should be documented. Other studies have also failed to observe a significant association between the use of blood transfusions and patients' fatigue levels [10, 11, 13, 24].

Regarding counselling for CRF, previous studies have reported that between 14% and 27% of cancer patients receive treatment or advice about the management of their fatigue [10, 25]. The relatively high percentage of patients in our study (more than 50%) reporting having received specific counselling on fatigue is notable. However, we found that most of the fatigue-related counselling was directed towards energy conservation, rather than enhancement of physical activity levels. Previous studies have also reported that fatigued patients are most commonly advised to rest and relax [10]. More recent studies suggest,

however, that physical activity and exercise may have a powerful, positive effect on fatigue. Conversely, reducing physical activity levels may lead to reduced levels of physical fitness and thus may exacerbate fatigue symptoms [6, 7]. For this reason, the current guidelines recommend efforts to increase levels of physical activity.

We would note that the nurses in our study were aware of the guidelines on counselling for fatigue and had, in fact, undergone continuing education in this area. However, this was apparently not sufficient to bring about a shift from recommending energy conservation to recommending activity enhancement. The seemingly counterintuitive finding that a greater percentage of patients without fatigue reported having been counselled on energy conservation may reflect a tendency by the nurses to counsel non-fatigued patients not to overexert themselves.

Several possible limitations of this study should be noted. First, patient self-report data were used to evaluate the counselling that patients' received. Ideally, evaluation of health care communication at the individual level is carried out using audiotapes or videotapes. This was not feasible in the current study due to both technical and privacy reasons. Although self-report data have their limitations, our previous study found that information provided by oncology patients about what was discussed during outpatient chemotherapy visits is quite accurate (when compared to information provided by observers) [26].

Second, despite the fact that this study is one of the largest of its kind, the sample size limited the statistical power available for some of the subgroup analyses. For example, with a larger sample, the marginal association observed between the use of epoetin and self-reported fatigue levels might have been more clearly significant.

Conclusions

Guidelines regarding medical treatment options for CRA or CRF are reasonably precise. Nevertheless, there is a reluctance to prescribe pharmacological treatments, even when they are recommended by published treatment guidelines. A variety of adherence barriers have been suggested in earlier studies, including the lack of awareness of the guidelines, disagreement with them, scepticism about the effectiveness of guideline-driven management, in general, lack of confidence in the ability to implement guidelines and inertia [27]. Given more recent findings regarding the potential dangers associated with the use of epoetins, some of this reluctance may be justified.

The guidelines on counselling for CRF could benefit from further clarification. First, they need to be reformulated into best practices, with the most successful counselling strategies being highlighted. In particular, the positive effects of activity enhancement need to be emphasised. Additionally, ongoing, repeated counselling may enhance its effectiveness, as has been shown in other patient populations [28]. Additionally, tailored counselling that takes clinical (e.g. stage of disease) and patient (age and gender) characteristics into consideration may further optimise its effectiveness.

Finally, the value of the guidelines on the treatment of CRA and CRF might be enhanced by explicitly recommending the use of self-reported measures to monitor fatigue in daily clinical practice. Integrating the assessment of commonly experienced symptoms such as fatigue into daily clinical practice may have important implications for improving symptom management [29]. Ideally, use of clinically relevant thresholds for patient-reported fatigue could be tied to appropriate clinical pathways for the treatment of CRA and CRF. Any future enhancements in counselling for CRF should be investigated empirically, preferably in the context of a randomised clinical trial, in order to establish a strong evidence base for such interventions.

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