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ORIGINAL ARTICLE

Patients' views about causes and preferences for the management of cancer-related fatigue—a case for non-congruence with the physicians?

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Abstract

Purpose Cancer-related fatigue (CRF) is frequently overlooked. Adherence to treatment guidelines may be related to the patient's views about illness. This study aimed at exploring patients' views about CRF and determining whether they are congruent with best practice treatments.

Methods Data were collected in 160 consecutive patients hospitalized in a supportive care setting. Biological, clinical, and psychological variables were assessed using validated questionnaires. Patients were also asked to complete the Brief Fatigue Inventory (BFI) and a questionnaire investigating their main symptoms and views about CRF and its management.

Results Patients were mainly men (60%); median age was 66 years. Various cancer diagnoses were represented; 17.5% had primary local diseases, 40% local recurrences, and 42.5% metastatic diseases. The majority of the patients experienced moderate or severe CRF (76.3%) on the BFI. Fatigue was the most frequently reported symptom (87.5%).

Only anxiety, depression, and dimensions of quality of life were significantly related with CRF. Two thirds of the patients associated CRF with cancer-related morbidities. As for the best treatments, patients first stressed control of adverse effects. Over half of the patients were reluctant to report fatigue, mainly because they considered fatigue as an unavoidable side effect, but also because they feared a change towards less active/aggressive treatments.

Conclusion Patients mostly consider that CRF must be tolerated. Guidelines emphasize activity enhancement strategies as beneficial. The patients' preferences for rest rather than activity may be related to their high level of fatigue, which leads them to disregard activity as a possible treatment.

Keywords Fatigue · Cancer-related fatigue · Supportive care · Patients' views · Treatment preferences · Treatment guidelines

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Introduction

Cancer-related fatigue (CRF) is defined as a persistent, subjective sense of weakness and tiredness, despite adequate rest, that interferes with usual functioning [1, 2]. However, there is no clear agreement on a scientifically based definition largely because the exact mechanisms causing fatigue are still in the early stages of investigation. A variety of mechanisms have been proposed for CRF, although none has been proven [3]. Physiological and psychosocial factors are recognized as playing a part [4, 5]. Contributors to fatigue cover a wide range of causes, including treatable conditions such as anemia, functional deconditioning, and adverse effects of treatments as well as other symptoms such as pain and depression [5].

CRF is a common problem for patients who are undergoing cancer treatment [6]. The true incidence of CRF is difficult to ascertain. Published studies are restricted to prevalence data. Estimates are that CRF affects between 17% and 90% of cancer patients overall [7–9]. More than 75% of the patients with advanced cancer are affected [8]. Furthermore, CRF has been described as a distressing symptom, even more than pain or nausea and vomiting [10]. Although CRF is identified by patients as a distressing symptom associated with cancer and its treatment, it is often overlooked as a potentially treatable problem [5, 11]. However, systematic reviews have shown the effectiveness of various interventions, pharmacological [12], physical via exercise [13], or psychosocial [14].

The clinical guidelines of the National Institutes of Health and the National Comprehensive Cancer Network (NCCN) put a major emphasis on the various aspects of the prevention and treatment of CRF [1, 2]. Management of CRF involves the assessment and the treatment of contributing factors (e.g., treating anemia, managing pain, or depression) resulting in specific pharmacological or non-pharmacological interventions (e.g., education, counseling, and exercise). However, the effective implementation of these clinical guidelines is difficult. Various studies suggest that adherence to treatment and recommendations is related to the patient's beliefs and expectations about illness and its management [15–17]. From the patient's perspective, non-adherence may be a more rational decision, based on his/her beliefs and previous experiences, than an irrational act of noncompliance [15]. This decision is dependent on the patient's weighing of the balance between his/her perception of the costs and benefits of the intervention. In this process, the doctors' point of view and the scientific evidence are not the only sources of information [18], and the personal and social circumstances within which they live play a crucial role in the patient's decision making. Agreement between the patients' views and the guidelines may thus be a crucial issue, insofar as the patients' beliefs and experiences about CRF may not be congruent with best practice treatments recommended in the guidelines. This is of special interest when it comes to enhancing the practical utility of these guidelines for the patients.

This study aimed to quantify and qualify CRF in hospitalized patients, to investigate patients' views about CRF, and to determine as to what extent patients' views are congruent with the best practice treatments described in the guidelines.

Methods

Setting The study was conducted at a cancer supportive care unit. This 12-bed facility is part of the Division of

General Medical Rehabilitation of the Geneva University Hospitals, a 96-bed internal subacute medical ward devoted to general medical rehabilitation and supportive care in cancer. The multidisciplinary staff of the supportive care unit is headed jointly by an oncologist and an internist. Consecutive cancer patients hospitalized in the supportive care unit during an 18-month period were investigated in the first 48 h of their admission. Inclusion criteria were patients ≥ 18 years old, undergoing an active cancer treatment and a sufficient knowledge of French to participate in the study. The study protocol was approved by the hospital Ethics Committee, and the study was performed in accordance with the ethical standards of the Declaration of Helsinki. All included patients gave their written informed consent.

Materials The Brief Fatigue Inventory (BFI) [19], specifically developed to measure fatigue in cancer populations, was used; this nine-item scale is user-friendly, and its psychometric properties have been well established [20]. The first three items deal with feelings of fatigue (right now, usual level, and worst level) over the past 24 h. These three items are numerical rating scales (NRS) graded from 0 (“no fatigue”) to 10 (“as bad as you can imagine”). The next six items deal with various activities of daily living, relationships, or quality of life experienced over the previous 24 h. These six items are also NRS graded from 0 (“does not interfere”) to 10 (“completely interferes”). A global index is then calculated by adding the scores of the nine items and dividing the sum by nine, for a final score comprised between 0 and 10. Level 0 indicates no fatigue; levels 1–3 indicate mild fatigue; levels 4–6, moderate fatigue; and levels 7–10, severe fatigue [20].

In addition, a five-item questionnaire was devised to evaluate the patients' perception of their main symptoms and impact on everyday life as measured on 11-point NRS, as well as the presence and type of problems related to the report of fatigue; the questionnaire also included the investigation of the patients' views about causes of fatigue and best/expected treatments. The multiple choice questions about causes and treatment of CRF were devised using the various domains of recommendations described as best evidence in the practice guidelines [1, 2]. The questionnaire was pretested on a subset of patients. The physicians' identification of the main symptoms of the patients on admission was compared to the patients' appraisal. This identification is routinely performed by the physicians in charge of the unit on the basis of the same items as those used in the patient questionnaire.

Along with these fatigue-specific measurements, other data were collected to allow for the characterization of the patients and of their disease and treatments. A comorbidity index (Charlson et al. [21]), laboratory data (hemoglobin

levels and serum biochemical variables), type and stage of cancer (primary local diseases, local recurrences, or metastatic diseases), chemotherapy and radiotherapy in the last 3 months, and medication intake at the time of the admission (analgesics, corticosteroids, antiemetics, anticonvulsants, antidepressants, and benzodiazepines) were extracted from the medical charts. Validated scales were used to assess functional status and health-related quality of life (Eastern Cooperative Oncology Group (ECOG) performance status [22], European Organisation for Research and Treatment of Cancer (EORTC)-Quality of Life Questionnaire for Cancer patients (QLQC)-30 [23]), as well as anxiety and depression (Hospital Anxiety and Depression Scale (HADS) [24, 25]).

Statistical methods Demographic and questionnaire data were analyzed using Chi-square tests for categorical data and *t* tests for continuous data. Pearson's correlation was used to compare BFI scores and clinical, psychosocial, and functional scales.

Results

Patient inclusion During the study period, 228 patients were recruited; 68 patients could not give an informed consent (poor fluency in French [$N=16$]; cognitive impairments [$N=14$]), or refused to participate [$N=38$]). Thus, 160 patients were included (Table 1); age ranged from 21 to 91 years old, with median age of 66 years.

Clinical characteristics of the patients A wide range of cancer diagnoses were represented (Table 1); 28 patients (17.5%) suffered primary local diseases, 65 (40%) local recurrences, and 67 (42.5%) metastatic diseases. Mean time since diagnosis was 1.5 years (range=0–12 years). Mean Charlson comorbidity index was 7.48 (SD=1.9). Mean hemoglobin level was 10.98 g/l (SD=1.6), and 21.9% of the patients had a hemoglobin level <10 g/l, indicating a moderate anemia. Patients had received various oncological treatments in the previous 3 months. Most of the patients were on analgesics, and a vast majority received benzodiazepines (Table 2). The vast majority of the patients (>80%) experienced functional limitations as assessed by the ECOG performance status. Similarly, the scores were low on the physical and role functioning subscales of the EORTC-QLQC-30. Nearly a third of the patients showed signs of psychiatric morbidity on the HADS (Table 1).

Prevalence and impact of fatigue and other symptoms The results of the BFI indicated that very few patients reported no fatigue ($N=19$; 11.9%) or mild fatigue ($N=19$; 11.9%),

whereas moderate and severe fatigue were reported by 70 (43.8%) and 52 (32.5%) patients, respectively.

On admission, patients were questioned about their main symptoms. They reported a mean of 3.8 symptoms/patient (SD=1.8); the most frequent were fatigue ($N=140$; 87.5%), pain ($N=72$; 45%), loss of appetite ($N=62$; 38.8%), sadness or anxiety ($N=61$; 38.1%), and dyspnea ($N=57$; 35.6%). The estimated mean impact of these symptoms was low for most of these symptoms except for fatigue, however. Indeed, on a 0 to 10 NRS, the impact ranged from 1.89 to 2.21, except for fatigue, which had a mean score of 5.8 (SD=3). Not surprisingly, the patients' perception of the impact of fatigue was highly correlated with the BFI (Pearson $r=0.923$; $p<0.0001$).

Bivariate correlations showed that among various clinical characteristics of the patients (e.g., stage of the disease, medication intake, and functional status), only anxiety and depression as well as self-reported functional scales and global evaluation of the quality of life were significantly related with fatigue as measured by the BFI (Table 2).

Patients' views on the causes and best treatments of fatigue Two thirds of the patients associated CRF with cancer-related morbidities and treatments, in particular, chemotherapy, radiotherapy, and surgery (Table 3). Among the main CRF contributing factors described in the guidelines, one third of the patients pointed to muscle loss, sleep disturbance, nutrition, and emotional distress, whereas physical activity and anemia were only rarely mentioned. Only one patient declared to have no opinion regarding the factors contributing to CRF. As for the best treatments of CRF, patients first stressed treatments aimed to control adverse effects of chemo- and radiotherapy, and to handle pain (two fifth of the patients); one third of them also mentioned managing nutritional deficiencies, pharmacological sleep therapy, and counseling for emotional distress; a similar proportion of patients (one fourth) suggested bed rest and progressive physical activity as best treatments for CRF (Table 3). Only few patients cited psychostimulants and pacing activities in the everyday life or during the hospital stay. None of these responses was significantly associated with the level of fatigue as measured by the BFI, except for managing nutritional deficiencies, which was significantly ($p<0.01$) more often mentioned by severely fatigued patients ($BFI\geq 7$).

Fatigue in the patient-physician communication The vast majority of the patients reported moderate or even severe fatigue with a high impact (5.8 on an 11-point NRS) on everyday life. However, the investigation of the presence and type of problems possibly related to the report of fatigue in the five-item questionnaire showed that 90

Table 1 Sociodemographic, clinical, and psychological characteristics of the patients

| | <i>N</i> (%) | Median (range) |
|--|--------------|----------------|
| Age | | 66 (21–91) |
| Gender | | |
| Men | 96 (60) | |
| Women | 64 (40) | |
| Education | | |
| Completed elementary school | 31 (19.4) | |
| Completed high school | 95 (59.4) | |
| Completed university | 34 (21.3) | |
| Charlson comorbidity index | | 7 (4–15) |
| Primary cancer site | | |
| Lung | 41 (25.6) | |
| Gastrointestinal | 30 (18.8) | |
| Head and neck | 18 (11.3) | |
| Urogenital | 17 (10.6) | |
| Breast | 13 (8.1) | |
| CNS | 8 (5) | |
| Hematological | 6 (3.8) | |
| Other | 16 (10) | |
| Oncological treatment before inclusion (<3 months) | | |
| Chemotherapy | 72 (45.3) | |
| Radiotherapy | 48 (30.2) | |
| Surgery | 45 (28.3) | |
| Hormonotherapy | 23 (14.5) | |
| Immunotherapy | 7 (4.4) | |
| Medication intake (admission) | | |
| Level I—acetaminophen | 146 (91.3) | |
| Level II—NSAIDs, weak opioids | 57 (35.6) | |
| Level III—strong opioids | 88 (55) | |
| Corticosteroids | 125 (78.1) | |
| Antiemetics | 71 (44.4) | |
| Antidepressants | 23 (14.4) | |
| Benzodiazepines | 129 (80.6) | |
| Fatigue score [BFI] | | |
| No fatigue | 19 (11.9%) | |
| Mild fatigue | 19 (11.9%) | |
| Moderate fatigue | 70 (43.8%) | |
| Severe fatigue | 52 (32.5%) | |
| Functional and emotional status | | |
| Functional status [performance status] | 1 (0.6) | |
| 0=fully active | 22 (14.0) | |
| 1=slightly impaired | 73 (46.5) | |
| 2=up and about >50% | 55 (35.0) | |
| 3=confined to bed >50% | 6 (3.8) | |
| 4=totally disabled | | |
| Functional scales [EORTC-QLQC-30] | | |
| Physical functioning | | 40.0 (0–100) |
| Role functioning | | 33.3 (0–100) |
| Emotional functioning | | 66.7 (0–100) |

Table 1 (continued)

| | <i>N</i> (%) | Median (range) |
|--|--------------|----------------|
| Cognitive functioning | | 66.7 (0–100) |
| Social functioning | | 58.3 (0–100) |
| Global QoL | | 58.3 (0–100) |
| Emotional status [HADS] (<i>N</i> =123) | | |
| Anxiety score ≥ 11 | 41 (33.3) | 9 (0–17) |
| Depression score ≥ 11 | 37 (30.1) | 8 (0–19) |

patients (56.3%) also reported to be uncertain whether to discuss fatigue with the physician. The main reasons for this reluctance were that they assumed that CRF is

unavoidable or a necessary adverse effect of cancer-related treatment (43% and 36% of responses, respectively), but they also stressed that they feared that their treatment

Table 2 Correlations between fatigue (Brief Fatigue Inventory) and clinical characteristics

| | Fatigue—Brief Fatigue Inventory |
|---|---------------------------------|
| Charlson | 0.058 |
| Performance status | 0.087 |
| Hemoglobin <10 g/l | 0.04 |
| Stage of disease | |
| Primary local disease | |
| Local recurrence | |
| Metastatic disease | |
| Time since Ca diagnosis | −0.14 |
| Prior oncological treatment (<3 months) | |
| Chemotherapy | 2.664 |
| Radiotherapy | 6.024 |
| Surgery | 0.640 |
| Medication use (admission) | |
| Antalgic level II | 1.927 |
| Antalgic level III | 0.785 |
| Corticosteroids | 2.818 |
| Antidepressants | 7.846* |
| Benzodiazepines | 3.223 |
| Self-reported main symptoms (admission) | |
| Fatigue | 0.923** |
| Pain | −0.068 |
| Loss of appetite | 0.129 |
| Dyspnea | 0.032 |
| Emotional distress | 0.004 |
| EORTC-QLQ-C30 | |
| Physical functioning | 0.158* |
| Role functioning | 0.205* |
| Emotional functioning | 0.029 |
| Cognitive functioning | 0.049 |
| Social functioning | 0.179* |
| Global quality of life | 0.219* |
| Fatigue (symptom subscales) | 0.374* |
| HADS anxiety | 0.205* |
| HADS depression | 0.290** |
| HADS total | 0.266** |

*Pearson correlation coefficient *p* value <0.05 (two-tailed)

**Pearson correlation coefficient *p* value <0.01 (two-tailed)

Table 3 Patients' assessment of the factors contributing to cancer-related fatigue (CRF) and of best/expected treatments for CRF

| Assessment | N (%) ^a | Treatment | N (%) ^a |
|---|--------------------|---|--------------------|
| Cancer-related morbidities, "cancer itself" | 108 (67.5) | Treating AE of cancer-related treatments | 69 (43.1) |
| Cancer-related treatments (chemo-, radiotherapy, and surgery) | 100 (62.5) | Pain management | 62 (38.8) |
| Loss of muscles | 60 (37.5) | Managing nutritional deficiencies | 51 (31.9) |
| Sleep disturbance | 55 (34.4) | Sleep therapy (pharmacological) | 49 (30.6) |
| Nutrition | 48 (30) | Counseling for emotional distress | 48 (30) |
| Emotional distress | 46 (28.8) | Bed rest | 44 (27.5) |
| Pain | 37 (23.1) | Progressive physical activity | 41 (25.6) |
| Non cancer-related morbidities | 22 (13.8) | Complementary medicine | 38 (23.8) |
| Physical activity | 21 (13.1) | Psychostimulants | 22 (13.8) |
| Anemia | 12 (7.5) | Planning of hospital stay (care, consultations, rest, exercises...) | 13 (8.1) |
| Others | 1 (0.6) | Prioritizing and pacing daily life activities | 7 (4.4) |
| I have no opinion | 1 (0.6) | Others | 3 (1.9) |

^a As more than one response was possible, the total is higher than 100%

may be altered if they reported fatigue (41%). The responses also showed that patients tended to believe that there is no treatment for CRF (28%) and that they may bother the physician with fatigue complaints (26%); furthermore, 26% of them indicated that physicians do not tackle this issue and/or that they preferred to discuss it with other health care providers (23%). Finally, 33% of the patients indicated that they felt reluctant to discuss fatigue with the physician but for no specific reason.

The comparison of the patients' appraisal of their main symptoms with the physicians' evaluation of the main symptoms of the patients on admission showed varying levels of agreement: the patients and the physicians of the supportive care unit agreed on the presence (or absence) of fatigue in 59.7% of the cases; fatigue was mentioned in 87.5% of the patients, whereas it was mentioned as a main symptom in 56% of the cases by the physician in charge. The agreement was 57.2% for sadness or anxiety and higher for loss of appetite (62.3%), pain (65%), and dyspnea (75.5%).

Discussion

The vast majority of the patients in this study experienced moderate or severe CRF. The impact of CRF was described as clearly more important than other self-reported symptoms, such as pain, loss of appetite, sadness or anxiety, and dyspnea. Despite the importance of fatigue, more than half of patients were reluctant to discuss it with the physician, mainly because they considered fatigue as an unavoidable side effect of both the disease and its treatment, but also because they feared a change toward a less active/aggressive treatment to accommodate fatigue.

The results of our study put a strong emphasis on the patient's weighing of the perceived costs and benefits not only of the interventions but also of discussing fatigue. These beliefs may act as barriers to communication about fatigue [15, 18]. Fatalistic attitudes about possible treatment of CRF have been stressed [11], and studies also suggest that the physicians often fail to recognize fatigue as a significant problem for the patient [11, 26, 27]. In line with this, our results indicate that hardly more than half of the physicians' and the patients' responses converged on fatigue as a main symptom, whereas it was mentioned as such in almost 90% of the patients.

It is noteworthy that all the patients had views to express about the reasons for CRF and the expected/best treatments. Responses encompassed representations of fatigue in terms of physical exhaustion, leading to solutions aiming at "recharging the battery" by eating, resting, and sleeping. Fatigue is a commonplace symptom and has highly varying degrees of severity; it comprises perceptions as diverse as "healthy fatigue" and CRF. This variety of perceptions refers both to physical sensations and to affective experiences. The affective component is not only determined by the sensation itself but also by the context: e.g., "feeling dead" may refer to the well-being related to what is commonly labeled a healthy fatigue due to (pleasant) physical activities. This attempt to "recharge the battery" and sort out the perceived physical and affective experiences of fatigue may contribute to the patients' difficulty to consider the recommendations regarding physical activity. The NCCN guidelines for CRF [1, 2] emphasize activity enhancement and energy conservation strategies as beneficial interventions for CRF. These strategies did not meet the patients' preferences, however. The patients' preference for bed rest and pharmacological sleep therapy rather than

progressive physical activity may be related to their high level of fatigue. Similarly, recommendations about prioritizing and pacing activities during the hospital stay or in everyday life were also overlooked.

Besides the frequent attribution of fatigue to cancer and its treatment, patients also pointed to causes identified as treatable contributing factors by the NCCN guidelines, in particular, nutrition, muscle loss, sleep disturbance, and emotional distress, but to a much lesser extent. Accordingly, managing nutritional deficiencies, pharmacological sleep therapy, and counseling for emotional distress were selected by the patients as the treatments they would rate best for themselves.

Clinically, symptoms such as pain, loss of appetite and dyspnea, or hemoglobin levels, were not correlated to fatigue, contrary to the results of other studies [28–31]. There was no correlation either with medication intake except for antidepressants. The relation between antidepressants and fatigue was probably mediated by anxiety, and depression as the indication for antidepressants in these patients was mainly depression and not other reasons such as pain for example. Various clinical and psychological characteristics were correlated with fatigue, but they did not refer to the status of the disease or to comorbidities but rather to the patient's evaluation of his/her distress and health-related quality of life. In the same line, fatigue was not correlated with the functional status as assessed by the care providers (ECOG performance status) but with the self-reported functional scales of quality of life questionnaire (EORTC-QLQ-C30). These results are congruent with other studies on the importance of psychological distress as a correlate of fatigue [32–34].

This study has limitations. It has been conducted in a teaching hospital, and it raises the question of the extent to which the results can be generalized to other settings. However, the clinical and psychological characteristics of the patients in our sample were similar to those of other supportive care settings [28]. Furthermore, the prevalence and severity of fatigue were comparable to the data obtained in other studies [4, 31]. This study is cross-sectional and does not allow establishing causal relationships.

CRF is a highly complex symptom both from the perspective of scientific and lay knowledge. Guidelines may take physician focus away from the patient's specific experience [35, 36] including patients' preferences about treatment. The results of this study emphasize the role of the health professionals in decoding the patients' fears and needs. It is difficult to talk about fatigue if it means a risk to get a less active treatment; it is difficult to recommend activity and movement if fatigue is associated with "too much": too much energy devoted to coping with the disease, its treatments, and adverse effects, too many fears that the disease is accelerating or that treatments might be

withdrawn. Clearly, the information patients need is not (only) the information provided in the guidelines or in the consent forms.

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Conflict of interest None.

The authors have full control of all primary data and agree to allow the journal to review their data if requested.

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