Review

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Fatigue in cancer patients receiving chemotherapy: an analysis of published studies

A. Iop*, A. M. Manfredi & S. Bonura

Oncology Unit, General Hospital, Latisana, Italy

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Fatigue is a subjective experience that affects everybody. In healthy individuals, it can be considered a physiological response to physical or psychological stress. In people with specific diseases, however, fatigue often represents one of the most significant problems. Fatigue can be caused by many factors, both intrinsic to the patient and extrinsic, such as therapeutic interventions. This review, based on published studies, has been conducted with the aim of presenting a critical discussion of the available information on the characteristics, causes and potential treatments of fatigue in cancer patients receiving chemotherapy. The incidence of fatigue in these patients, the methods for measuring and evaluating fatigue, and possible therapeutic options are discussed. An appraisal of the toxicity of various chemotherapeutic agents is also presented. Although fatigue is now an ever more considered aspect of the toxicity of chemotherapy, it remains difficult to establish what standard should be used to make a quali-quantitative evaluation of this symptom. Furthermore, in the absence of a clear demonstration of the efficacy of some therapies, the management of cancer-related fatigue remains poorly defined (except for the treatment of anemia-related fatigue). New randomized clinical trials are necessary to indicate the best strategies for tackling this important problem.

Key words: chemotherapy, fatigue, toxicity

Introduction

Fatigue is a common problem in patients receiving treatment for cancer. This type of fatigue, defined as cancer- or therapy-related, is different from everyday tiredness, which can be reversed by rest or sleep. Until recently cancer-related fatigue has been overlooked by patients and health-care personnel, and only the growing attention to the quality of life of patients with cancer has begun to contribute to a re-evaluation of this symptom. In recognition of its importance, cancer-related fatigue was recently classified as an independent nosological entity in the 10th revision of the International Classification of Diseases (year 2000). Nevertheless, knowledge about this condition remains fragmentary and scarce. The aim of this review is to present a critical discussion of the available information on the characteristics, causes and potential treatments of fatigue.

Through careful analysis of the documentation, we have quantified the impact of fatigue, maintained or caused by chemotherapeutic agents administered alone or in association, to categorize them in the therapeutic management algorithm for cancer patients.

Fatigue has been described in the literature as tiredness, exhaustion, depression, feeling unwell, loss of motivation and limitations of mental state [1–3]. Furthermore, it has been demonstrated that fatigue reduces the individual resources of patients [4], influences their nutritional state, increases morbidity [5] and can negatively affect the dose intensity of some forms of oncology therapy [6].

Fatigue is a multifaceted, subjective condition. It can be described using a range of general characteristics (severity, negative sensations, temporal features) and specific weaknesses (lack of energy, weakness, somnolence, difficulty in concentrating). Fatigue can be defined as a multidimensional phenomenon which evolves over time, compromising physical energy, mental capacity and the psychological condition of the patient with cancer (Table 1) [7].

Fatigue associated with cancer probably has both physical and psychological causes; the former include anemia, various metabolic disturbances and inappropriate nutrition due to anorexia, nausea, vomiting or gastro-intestinal obstruction. The psychological factors which may contribute to fatigue include depression, anxiety and lack of sleep. Finally, the release of endogenous inflammatory cytokines contributes to the severity of fatigue in some patients [8].

There are various factors which potentially predispose to or cause cancer-related fatigue (Table 2). Several studies have shown a correlation between fatigue and different types of oncological therapy. It is known that fatigue is the commonest side-effect of chemotherapy and radiotherapy: it has been shown that 65–100% of patients undergoing radiotherapy [9–11] and up to 82–96% of those receiving chemotherapy [12, 13] suffer from fatigue during their treatment.

Correspondence to: Dr A. Iop, Oncology Unit, General Hospital, 33053 Latisana, Udine, Italy. Tel: +39-0431-529298; Fax: +39-0431-520478; E-mail: onco-lat@ass5.sanita.fvg.it

Table 1. Proposed criteria for diagnosing cancer-related fatigue [7]

The following symptoms have been present every day or nearly every day during the same 2-week period in the past month:
Significant fatigue, diminished energy or increased need of rest, disproportionate to any recent change in activity level.
Plus five (or more) of the following:
(a) complaints of generalized weakness or limb heaviness;
(b) diminished concentration or attention;
(c) decreased motivation or interest in engaging in usual activities;
(d) insomnia or hypersomnia;
(e) experience of sleep as unrefreshing or nonrestorative;
(f) perceived need to struggle to overcome inactivity;
(g) marked emotional reactivity (e.g. sadness, frustration or irritability) to feeling fatigued;
(h) difficulty in completing daily tasks attributed to feeling fatigued;
(i) perceived problems with short-term memory;
(j) post-exertionial malaise lasting several hours.
The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
There is evidence from history, physical examination or laboratory findings that symptoms are a consequence of cancer or cancer-related therapy.
The symptoms are not primarily the consequence of comorbid psychiatric disorders, such as major depression, somatization disorder, somatoform disorder or delirium.

As could be imagined, fatigue is correlated to the intensity of treatment, and becomes a relevant toxic effect the more the treatment intensity is increased. This correlation could be predictive of the fatigue observed at some time after treatment. In their review, Jacobsen and Stein [14] observed that patients with breast cancer who were treated with adjuvant chemotherapy or autologous bone marrow transplantation complained of significant levels or fatigue for months or even years after the completion of therapy. Conversely, this long-term effect is much less frequent in patients who undergo only loco-regional treatments.

Two investigations on the impact of fatigue on the quality of life of cancer patients were carried out by the Fatigue Coalition, a multidisciplinary group whose aim was to examine the importance of fatigue in patients and their caregivers, and to draw up guidelines on the diagnosis and treatment of the fatigue syndrome. Vogelzang et al. carried out a telephone investigation in 419 randomly selected patients who had received chemotherapy or radiotherapy, and also in their caregivers and oncologists [15]. Fatigue was reported by 78% of the patients during the course of their disease or during treatment, and about one-third reported daily fatigue and difficulty in carrying out normal daily activities.

From a different perspective, fatigue was noticed by 86% of the patients' caregivers, while 76% of the oncologists recorded this syndrome in their patients. Furthermore, 80% of the oncologists considered that fatigue was ignored or not adequately treated, while 74% of the patients considered that it was a symptom that had to be put up with. Fifty per cent of the patients did not discuss therapeutic options with their oncologists, and only 27% said that their oncologist had prescribed or advised them on some sort of treatment for the fatigue.

A second telephone survey by the Fatigue Coalition confirmed that fatigue was common in patients who received chemotherapy, and that it had detrimental physical, psychosocial and financial consequences (Table 3) [16].

More than half of the patients had suffered fatigue every day or almost every day. Nevertheless, even social activities, concentration and caring for the family were more difficult for >50% of patients on the days when they suffered from fatigue. An analysis of the financial impact of this syndrome revealed that 75% of patients had changed their employment status. Bed rest and relaxation techniques were the treatments most widely advised by doctors; nevertheless, 40% of patients were not provided with any advice or recommendation.

Incidence of fatigue in patients undergoing chemotherapy

Only in relatively recent times has the clinical picture of fatigue been assimilated into the field of oncology, and indeed its evaluation is still often not included among the parameters normally used to describe the toxicity of chemotherapy. With these limitations, we have identified recently published articles that report fatigue (or symptoms similar to it, such as asthenia) among the descriptors of toxicity of chemotherapeutic agents, dividing the various articles according to the underlying malignancy (Tables 4–9).

In most cases toxicity was graded using the National Cancer Institute Common Toxicity Criteria (NCI CTC) scale, which

Table 2. Potential predisposing factors or etiologies of cancer-related fatigue [7]

Physiological
Underlying disease
Treatment for the disease
Chemotherapy
Radiotherapy
Surgery
Biological response modifiers
Intercurrent systemic disorders
Anemia
Infection
Pulmonary disorders
Hepatic failure
Heart failure
Renal insufficiency
Malnutrition
Neuromuscular disorders
Dehydration or electrolyte disturbances
Sleep disorders
Immobility or lack of exercise
Chronic pain
Use of centrally acting drugs (e.g. opioids)
Psychosocial
Anxiety disorders
Depressive disorders
Stress-related
Environmental reinforcers

places fatigue among constitutional symptoms including other clinical pictures, such as lethargy, generalized sense of feeling unwell and asthenia. The classification of the grades of toxicity in the updated version of the NCI CTC is summarized in Table 10.

From the analysis of the published data, it emerged that low-grade fatigue (defined as such or under other headings) is present in ~30% (on average) of treated patients, while only ~10% report severe grade fatigue. All this is obviously in the context of variability associated with the type of patient, the type of neoplasia (which does not, however, seem to influence the degree of fatigue significantly), the treatment and the dose intensity of the chemotherapy.

Methods of evaluating and measuring fatigue

Over the last few years, various methods of evaluating and measuring fatigue have been proposed or introduced.

The Brief Fatigue Inventory is one of the methods developed to study fatigue [17]. This instrument evaluates fatigue over 24 h using a scale from 1 to 10 (1 indicates absence of, and 10 the worst imaginable fatigue). Studies have shown that values of 7 or above are strongly correlated with a clinically relevant level of difficulty.

Another instrument for evaluating fatigue is the MFI-20, a 20-item questionnaire which examines the following parameters: 'general', 'physical' and 'mental' fatigue, decreased motivation and reduced activity, through five subscales of five items each [18]. Using this method, Holzner et al. recently confirmed the correlation between hemoglobin levels, fatigue and quality of life in cancer patients [19].

The National Comprehensive Cancer Network (NCCN) Fatigue Practice Guidelines Panel reviewed the available evidence and the consensus of doctors managing fatigue to produce guidelines for clinical practice. Five factors were identified as being associated with fatigue: anemia, pain, emotional stress, sleep disturbances and hypothyroidism [20].

Using the Functional Assessment of Cancer Therapy–General (FACT–G) questionnaire, which measures overall quality of life (QoL), as a basis, 20 new questions have recently been developed concerning the impact of fatigue and other symptoms associated with anemia in cancer patients. Thus two new instruments have been constructed: FACT–Fatigue (FACT–F), made up of FACT–G and an additional 13 questions on fatigue (the 'fatigue' subscale) and FACT–Anemia (FACT–An), comprising FACT–F and a further seven questions on other aspects relevant to anemia but not to fatigue.

FACT–An, FACT–F and the fatigue subscale have been shown to be able to discriminate successfully between cancer patients on the basis of their levels of hemoglobin and performance status. Dividing the patients into two groups according to their levels of hemoglobin, those who had levels of hemoglobin >12 g/dl reported less fatigue and fewer symptoms of anemia, better phy-

Table 3. The impact of fatigue: results of a survey by the Fatigue Coalition [16]

Physical impact	Financial impact	Social and emotional impact
Difficulty in carrying out tasks, 56%	71% of patients lost one or more days of work	59% reported difficulty in socializing with friends and family
Difficulty in climbing stairs, 56%	31% lost an entire week of work	37% had difficulty in maintaining relationships
Difficulty in walking long distances, 69%	28% had to stop work	30% found intercourse with partner difficult
Difficulty in continuing exercise, 67%		

Table 4. Incidence of fatigue (or related symptoms) in patients receiving chemotherapy for non-small-cell lung cancer

Author [ref.]	Therapeutic regime	No. of patients	Fatigue grade, %	
			1–2	3–4
Sandler [33]	Gemcitabine + cisplatin	260	58	
Gatzemeier [34]	Taxol + cisplatin	207	68	
Wozniak [35]	Vinorelbine + cisplatin	204	30	
Shepherd [36]	Taxotere 75	55	36.3	18.2
	Taxotere 100 (second line)	49	38.8	22.4
Millward [37]	Taxol	51	25	0
Langer [38]	Taxol + carboplatin	53	58	21
Kosmas [39]	Gemcitabine + vinorelbine (second line)	40	13	0
Laack [40]	Gemcitabine + vinorelbine	70	41	1
Georgulias [41]	Taxotere + cisplatin	205	59	7
	versus			
	Taxotere + gemcitabine	201	62	6
Gridelli [42]	Vinorelbine	43	19	
Schiller [43]	Cisplatin + taxol	288	NA	14
	versus			
	Cisplatin + gemcitabine	288	NA	17
	versus			
	Cisplatin + taxotere	289	NA	16
	versus			
	Carboplatin + taxol	290	NA	15

NA, not available.

Table 5. Incidence of fatigue (or related symptoms) in patients receiving chemotherapy for small-cell lung cancer

Author [ref.]	Therapeutic regime	No. of patients	Fatigue grade, %	
			1–2	3–4
Ardizzoni [44]	Topotecan (second line)	93	35.9	3.4
Hainsworth [45]	Taxol + carboplatin + etoposide	38 low dose	NA	0
		79 high dose	NA	10
Thomas [46]	Taxol + carboplatin	48	3	1
Von Pawel [47]	Topotecan	107	21.5	4.7
	versus			
	Cyclophosphamide + doxorubicin + vincristine (second line)	104	25	8.7
Hainsworth [48]	Taxol + carboplatin + topotecan	105	11[a]	
			13[b]	

[a]During the first two cycles.
[b]In limited stage during chemoradiotherapy.
NA, not available.

sical and functional wellbeing, as well as a higher overall QoL [21].

The Linear Analog Scale Assessment (LASA) was recently used to measure the effect of therapy with epoetin α on parameters relating to QoL. Patients reported their level of energy, capacity to carry out daily activities and overall QoL on a scale from 0 (lowest value) to 100 (highest value). LASA is a unidimensional scale that is easy to use in clinical practice, and its results corres-

Table 6. Incidence of fatigue (or related symptoms) in patients receiving chemotherapy for ovarian cancer

Author [ref.]	Therapeutic regime	No. of patients	Fatigue grade, %	
			1–2	3–4
Markman [49]	Cisplatin i.v. + taxol i.v.	227	NA	1
	versus			
	Carboplatin i.v.+ taxol i.v. + cisplatin i.p.	235	NA	4
Creemers [50]	Topotecan (second line)	111	27.9	1.8
ten Bokkel Huinink [51]	Topotecan	112	33.1	8.0
	versus			
	Taxol	114	25.4	6.1
Gordon [52]	Liposomal doxorubicin	89	41.6	

NA, not available.

Table 7. Incidence of fatigue (or related symptoms) in patients receiving chemotherapy for colorectal cancer

Author [ref.]	Therapeutic regime	No. of patients	Fatigue grade, %	
			1–2	3–4
Schilsky [53]	Eniluracil + 5-fluorouracil	485	35	41
	versus			
	5-Fluorouracil + folinic acid	479	5	6
Punt [54]	5-Fluorouracil + leucovorin	182	NA	7
	versus			
	Trimetrexate + 5-fluorouracil + leucovorin	182	NA	4
Cassidy [55]	Capecitabine	596	21.1	
	versus			
	5-Fluorouracil + leucovorin	593	25	
Cascinu [56]	Raltitrexed + oxaliplatin	58	37	16
Saltz [57]	Irinotecan + 5-fluorouracil + leucovorin	225	8	
	versus			
	5-Fluorouracil + leucovorin	219	20	
	versus			
	Irinotecan	223	NA	
Van Cutsem [58]	Capecitabine (continuous)	39	23	0
	versus			
	Capecitabine (intermittent)	34	24	3
	versus			
	Capecitabine + leucovorin	35	18	0

NA, not available.

pond well (>70%) with those of the multidimensional FACT–An scale.

Piper's fatigue scale was the first validated multidimensional scale; it addresses the severity, distress and impact of fatigue using a 40-item questionnaire [22].

The Multidimensional Fatigue Symptom Inventory (MFSI) evaluates global, somatic, affective, cognitive and behavioral symptoms of fatigue through 83 items. It was administered to women who had received or were undergoing treatment for breast cancer. The MFSI appears to be sensitive to fatigue, accurately

Table 8. Incidence of fatigue (or related symptoms) in patients receiving chemotherapy for breast cancer

Author [ref.]	Therapeutic regime	No. of patients	Fatigue grade, %	
			1–2	3–4
Jones [59]	Vinorelbine	115	30	4
	versus			
	Melphalan	64	19	3
Batist [60]	Liposomal doxorubicin + cyclophosphamide	142	NR	6
	versus			
	Doxorubicin + cyclophosphamide	155	NR	5
Chan [61]	Docetaxel	161	45.2	14.5
	versus			
	Doxorubicin	165	44.1	12.3
Esteva [62]	Docetaxel + trastuzumab	30	62	20
O'Shaughnessy [63]	Capecitabine + docetaxel	255	NR	8.4
	versus			
	Docetaxel	256	NR	11
Nisticò [64]	Epirubicin + vinorelbine	52	53.5	13.5
Pagani [65]	Epirubicin + docetaxel	70	Gr≥2	8
Del Mastro [66]	HDCEF14	77	60	6.7
	versus			
	CEF21	74	52.8	2.8

NR, not reported.

Table 9. Incidence of fatigue (or related symptoms) in patients receiving chemotherapy for advanced head and neck cancer

Author (ref.)	Therapeutic regime	No. of patients	Fatigue grade	
			1–2	3–4
Colevas [67]	Docetaxel + cisplatin + fluorouracil+ leucovorin	30	29	1
Posner [68]	Docetaxel + cisplatin + fluorouracil	43	NR	2
Shin [69]	Taxol + ifosfamide + carboplatin	56	52	6

NR, not reported.

discriminating cancer patients from control subjects and between patients with varying levels of performance status [23].

Treatment of cancer-related fatigue

The potentially useful treatments for cancer-related fatigue are as follows: varying the patient's therapeutic regime; correcting metabolic disorders; and treating depression and insomnia. Furthermore, many physicians advise light physical exercise (a loss of muscle mass has been hypothesized to be a concausal mechanism of fatigue).

Recent controlled studies have shown that aerobic exercises prevent worsening fatigue and psychological stress in patients receiving high-dose therapy [24]. Furthermore, in women with breast cancer receiving chemotherapy, exercise can significantly reduce the level of fatigue, and as the duration of exercise increases, the intensity of fatigue declines [25]. In patients with melanoma receiving interferon-α, the combination of exercise and methylphenidate showed a positive effect on interferon-induced fatigue [26].

Other non-pharmacological therapeutic approaches include modifications in periods of activity and rest, cognitive therapy, behavioral therapy to modify sleep (sleep hygiene) and nutritional support.

Pharmacological treatments include central nervous system stimulants and corticosteroids. The use of the former is essentially

Table 10. Classification of the grades of fatigue in the updated version of the NCI CTC

Grade 1	Grade 2	Grade 3	Grade 4
Increased fatigue in relation to the baseline situation, but without interfering with normal activities	Moderate fatigue (e.g. worsening of performance status by 20% for the Karnofsky score or by one point in the ECOG scale) or difficulty in carrying out some activities	Severe fatigue (e.g. worsening of the performance status by 40% for the Karnofsky score or by two points in the ECOG scale) or loss of capacity to carry out some activities	Bed bound or severe disability

ECOG, Eastern Cooperative Oncology Group; NCI CTC, National Cancer Institute Common Toxicity Criteria.

empirical; there are no published studies in which the reduction of the level of fatigue was the primary end point. Recently, a psychostimulant, methylphenidate (Ritalin), has shown some activity in improving fatigue, sedation and pain in cancer patients [26, 27]. It has been hypothesized that the use of antidepressants, such as selective serotonin re-uptake inhibitors, could play a role in the treatment of fatigue, but again, there are no published data confirming this.

All this has led to a growth in the parallel market of alternative therapies. Many patients take chemical supplements of unproven efficacy. A recent study in HIV-positive patients reported that the two factors predicting use of these supplements were high educational level and marked degree of fatigue [28]. A similar investigation in cancer patients would probably find the same results. This highlights the need for controlled clinical studies which correctly evaluate the therapeutic approaches adopted for fatigue.

Anemia is recognized as one of the main potential causes of cancer-related fatigue: a review of the data of patients undergoing anticancer therapy showed that most of them were anemic or developed anemia during treatment [29]. Numerous clinical studies have shown that the administration of epoetin-α is a safe and effective way to correct anemia and significantly improve QoL in cancer patients [30].

Indeed, as demonstrated by LASA and FACT-An, both QoL and fatigue showed improvements which were proportional to hemoglobin increase and to response to chemotherapy in an independent manner [31]. Multivariate regression analyses from double-blind trials also confirm the benefit in QoL obtained increasing hemoglobin levels with epoetin-α [32].

Conclusions

In conclusion, although fatigue is now an increasingly considered aspect of the toxicity of chemotherapy, in part because of its impact on patient's QoL, it remains difficult to establish what standard should be used for the quali-quantitative evaluation of this symptom. Furthermore, in the absence of clear demonstration of the efficacy of some therapies and the present climate of empirism, therapeutic management of fatigue remains poorly defined (except for the treatment of anemia, which in its turn is a possible concause of fatigue).

More efforts, in the form of randomized clinical trials, are necessary so that in the near future the best strategies for tackling this important problem can be indicated.

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