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Role of psychological and emotional factors in cancer related fatigue (CRF) syndrome in advanced NSCLC patients undergoing palliative chemotherapy

Abstract

Background: Cancer-related fatigue syndrome (CRF) is observed in most cancer patients, especially in those with advanced disease. Pathomechanism of CRF is complex and not fully understood. The aim of the study was to determine the role of psychological and emotional factors in CRF in non small-cell lung cancer (NSCLC) patients at advanced stage of the disease undergoing chemotherapy.

Material and methods: 76 patients with locally advanced or metastatic NSCLC, undergoing palliative chemotherapy participated in the study. Prior to, during and after the treatment, the patients were asked to complete psychological questionnaires, like HADS, CERQ and daily diary constructed for the purpose of this study.

Results: Coping strategies like concentrating on other positive aspects and acceptance are factors, which positively, while catastrophising, anxiety and depression – negatively, characterise the level of perceived cancer related fatigue.

Conclusions: Results show that some coping and emotional strategies as well as psychological features may constitute predictors for CRF. It may suggest that psychological features can influence the performance status of patients and reduce fatigue perceived by patients. Further research is needed to fully explained the phenomenon.

Key words: cancer related fatigue syndrome (CRF), NSCLC, coping strategies with disease

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Introduction

According to the World Health Organization, lung cancer is the most common malignancy worldwide since every year about 1 200 000 new cases of the disease are reported. Lung cancer is also one of the most frequent causes of death [1]. Namely, the report from 2008 reveals that lung cancer is now the forth cause of death in high-income countries, the fifth in middle-income countries, and the eighth globally. In Poland five-year survival of lung cancer patients is as low as 14% [2].

Cancer related fatigue syndrome (CRF) has not received a single and comprehensive definition yet. One of them proposed by Cella et al [3], based on the most widely known features of fatigue, says that it is "a subjective state of an intensive and sustained exhaustion and reduced capacity for physical and mental work, which do not disappear after the rest".

Cancer related fatigue occurs in 70–100% of patients undergoing different types of anticancer therapy [4, 5]. Approximately 60–90% of patients suffer from CRF during chemotherapy, and 75–100% in the case of radiation treatment [6]. The incidence of CRF is not limited exclusively to patients with poor performance status (PS). Symptoms of this syndrome are also observed in patients with good and very good PS (WHO 0–1) as well [4, 5]. The frequency of CRF usually increases during chemotherapy, however in patients with small cell lung cancer administration of such a treatment results in reducing the incidence of CRF [7].

Consequences of CRF for cancer patients are very serious — they affect the physical life, but also - psychological and social ones. This syndrome leads to a reduction in daily activities in more than 80% of cancer patients. That weakness, often called by the patients "fatigue", lowers their ability to concentrate, thus additionally obstructing their daily functioning. Weakness experienced by cancer patients is not relieved by rest or sleep [8], however it is not the only symptom of CRF. *The National Comprehensive Cancer Network Fatigue Practice Guidelines* distinguished seven factors, which have been identified as the most common in the pathogenesis of cancer fatigue: pain, emotional distress, sleep disturbances, anaemia, nutrition deficiencies, reduced physiological adaptability and diseases co-occurrence [9]. Cancer related fatigue has been treated as a set of various symptoms occurring for a long time. In the group of 51 lung cancer patients who successfully underwent chemotherapy, the intensity of the whole group of factors, such as fatigue, cancer, depression and pain was evaluated. Results indicate that fatigue was the most frequently emerging symptom, strongly correlated with depression. Both of these symptoms accounted for 29% of the variance of quality of life ($p < 0.01$) [10].

Pathomechanism of CRF development has not been explicitly explained as yet [11, 12]. Cancer related fatigue is often directly related to either the progression of cancer or anticancer treatment, such as chemo-and/or radiotherapy. One of the better recognized factors predisposing to the development of CRF is anaemia. Polish study (POLCAS) involving patients receiving chemotherapy or chemoradiotherapy revealed that 31% of them suffered from anaemia prior to the treatment, while it occurred in 54% of the patients after the treatment cessation. In the case of lung cancer patients, anaemia was recognised in one third of them prior to the treatment and in as much as 75% of the patients after the treatment administration [13]. However, not every patient with anaemia suffers from weakness [12, 14, 15]. Of note, intensity of weakness in patients with anaemia also correlates with such symptoms as anxiety, depression, pain or shortness of breath [16]. In a pilot study, where 24 cancer patients undergoing palliative radiotherapy were asked to complete a series of psychological questionnaires prior to and after the treatment, results showed correlation between temperament and strategies of coping with disease with the level of fatigue [17].

Cancer related fatigue syndrome is one of the dominant complaints reported by patients with cancer, including lung cancer. Unfortunately, only a few studies provided compelling evidence on the effective treatment of this syndrome. Among the promising treatment options of CRF are e.g. therapies based on physical exercises, administration of recombinant human erythropoietin, psychotherapeutic and psychosocial interventions, and pharmacological stimulation. Other solutions, such as therapy with growth hormone, androgen, L-carnitine, or anti- inflammatory agents must be treated as pilot concepts, which could be implemented exclusively in the context of controlled clinical trials [7].

Objective of the study

The aims of the study were to obtain answers to the following questions:

— does NSCLC patient's emotional state characterise the subjective perception of CRF level during palliative chemotherapy?

— do the strategies for coping with the disease applied by the patients impact the subjective perception of CRF?

Table 1. Group characteristic according to clinical stage of the disease: Staging of Non-small Cell Lung Cancer based on 6th edition of that classification used

	Total	Women	Men
IIIA	10 (13.2%)	5 (17.2%)	5 (10.6%)
IIIB	17 (22.4%)	5 (17.2%)	12 (25.5%)
IV	49 (64.5%)	19 (65.5%)	30 (63.8%)
Total	76 (100.0%)	29 (100.0%)	47 (100.0%)

— what are the differences in positive and negative psychological features of fatigue perceived by lung cancer patients?

Material and methods

Participants

The study was conducted in two oncology clinics: Lung & Thoracic Tumours Department, The Maria Sklodowska-Curie Memorial Cancer Centre & Institute, Warsaw, Poland, and 3rd Pulmonary Clinic, National Tuberculosis & Lung Diseases Research Institute, Warsaw, Poland, in the period from July 2007 to January 2010. Patients diagnosed with locally advanced or metastatic NSCLC, with performance status (PS) according to ECOG/WHO from 0 to 2, and qualified for palliative chemotherapy were included into the study. The study was a prospective, non-interventional and observational one. It was designed for 7 visits: six, during routine control visits when patients were given the standard palliative treatment — multidrug chemotherapy and seventh — follow-up visit — 6–8 weeks after the therapy cessation. Only those patients who had received at least 3 cycles of chemotherapy were invited for the follow-up visits. The following variables were chosen for this analysis: emotional and psychological traits and strategies. During the study, patients were filling in the set of psychological questionnaires, namely: Cognitive Emotion Regulation Questionnaire (CERQ), The Hospital Anxiety and Depression Scale (HADS) and specially prepared for this particular study patients' daily diary for self-assessment of fatigue level. The patients were able to self-fill daily diaries and a set of psychological questionnaires.

At the first visit 76 patients at the age ranged 42–78 (M = 60.68 years, SD = 8.09) were enrolled, while 51 patients participated (M = 60,73 years; SD = 8.41) in follow-up visit. The group constituted from 38.16% women and 61.84% men. The most common causes of earlier termination of the treatment were disease progression (N = 18; 23.7%) and adverse events occurrence resulted from the treatment (N = 17; 22.4%). Two patients died (2.6%) and two resigned from participation in the study prior to the follow-up visit (2.6%). The study group was characterized by various clinical stage of the disease (Table 1).

Approximately half of the patients (51%) who underwent the whole treatment (all six cycles of chemotherapy), completed the survey with good performance status (PS = 0), 41% respondents with PS = 1, and 5,9% of them with PS = 2. One patient during the follow-up visit was in PS = 4.

The study was approved by the Ethical Review Board (R-I-002/238/2007) of Medical University of Białystok, Poland. Written consent was obtained from the patients.

Measures

In the study document analysis methods based on the questionnaire prepared for the sake of the study were employed, as well as questionnaire methods, i.e. standardised psychological questionnaires:

— Cognitive Emotion Regulation Questionnaire (CERQ) constructed by Garnfelski, Kraaji and Spinhoven in 2001 [18], in Polish adaptation by Marszał-Wiśniewska and Fajkowska-Stanik (2007). It allows for measuring 9 cognitive emotion regulation strategies: blaming yourself, blaming others, catastrophising, rumination, acceptance, concentration on other positive aspect, concentration on planning, positive reinterpretation and putting into perspective. In addition, these strategies can be divided into two groups: adaptive and non-adaptive [19]. The questionnaire was completed by the patients at each visit;
— The Hospital Anxiety and Depression Scale (HAD Scale) by Zigmond and Snaith (1983), in the Polish adaptation by Majkowicz, de Walden-Gałuszko and Chojnacka-Szawłowska (1994) [18]. The scale contains 14 questions with 4 response options. The scale was completed by the patients participating in the study at each visit;

— Self-assessment Health Diary — a tool created specifically for this study to measure subjective (perceived by patients) level of fatigue and symptoms accompanying the disease during chemotherapy and a follow-up visit. Patients were asked to observe themselves and assess the weakness level (4 questions) daily and the state of weakness during the last week (8 questions). Answers to the questions related to the fatigue level were coded on a 5-point Likert's scale (*Cronbach alpha* $\alpha = 0.854$).

Statistical methods

Statistical analysis was performed with the use of the statistical package SPSS 14PL, 18PL and 17EN. Results were considered significant when *p-value* < 0,05. In addition, due to a relatively small studied group, the tendency of the results was analysed as well, with the *p-value* < 0,1.

For statistical analysis basic descriptive statistics and multiple stepwise linear regression were employed.

Results

Linear stepwise regression analyses were employed for searching for predictors of CRF occurrence among the psychological and emotional variables. A stepwise regression analysis showed that in the first two cycles of therapy a lack of ability to use "concentration on the other positive aspects" strategy is an important predictor of CRF occurrence. At a later stage of the treatment higher catastrophising and lack of acceptance of the disease as well increasing levels of anxiety and depression are predictors of CRF occurrence (Table 2 and 3).

It is noteworthy that at later cycles of chemotherapy predictors are stronger than those at the beginning of the treatment and that fact might be important for the interpretation of the results. Therefore, early stage of the therapy may possibly be more important for psychological intervention.

Discussion

The questions among psychological and emotional patients' profile, predictors of perceived CRF were investigated. The analysis showed that the positive (constructive) strategies for coping with the disease, are predictor of lower-level of CRF, while negative strategies, such as catastrophising, may cause a higher perception of the fatigue. This may suggest that through the influence on patients' perception of illness and e.g. implementation of special training for patients, teaching them constructive strategies of coping with the situation of stress-induced cancer, it would be feasible to amend the perceived fatigue in NSCLC patients.

It should be emphasized that the study had an exploratory nature. An undoubted advantage of this study was an attempt to include subjective nature (patients assessment and perception) of CRF syndrome, because as yet medical components were unable to explain the whole characteristic of this phenomenon. Consequently, it would be

Table 2. Emotional and psychological predictors of cancer related fatigue in NSCLC patients undergoing chemotherapy

Cycle	Model	*R*	R^2	Adjusted R^2	Model summary — Changes statistics				
					Diff. R^2	*F Diff.*	df_1	df_2	*p*
1	1	.243[a]	0.059	0.046	0.059	4.641	1	74	0.034
2	1	.302[b]	0.091	0.079	0.091	7.231	1	72	0.009
3	1	.393[c]	0.155	0.138	0.155	9.342	1	51	0.004
4	1	.315[d]	0.099	0.076	0.099	4.285	1	39	0.045
5	1	.584[e]	0.341	0.281	0.341	5.698	1	11	0.036
	2	.784[f]	0.615	0.538	0.274	7.104	1	10	0.024
6	1	.893[g]	0.797	0.774	0.797	35.244	1	9	0.000
FU	1	.312[h]	0.098	0.079	0.098	5.193	1	48	0.027

[a]Predictors at visit 1 (v1): (constant), concentrating on other positive aspect; [b]Predictors at visit 2 (v2): (constant), concentration on other positive aspect; [c]Predictors at visit 3 (v3): (constant), anxiety; [d]Predictors at visit 4 (v4): (constant), depression; [e]Predictors at visit 5 (v5): (constant), anxiety; [f]Predictors at v5: (constant), anxiety, acceptance; [g]Predictors at visit 6 (v6): (constant), Catastrophising; [h]Predictors at follow-up visit (FU): (constant), depression; Dependent variable: Cancer related fatigue (CRF) at v1, v2, v3, v4, v5, v6 & FU; R —regression coefficient; R^2 — the coefficient of determination; F — Fischer statistic; Diff. — difference; *df* — degrees of freedom; *p* — p-value

Table 3. Coefficients of regression for emotional and psychological predictors of the perceived cancer related fatigue level in NSCLC patients undergoing chemotherapy

Cycle	Model		Non-standard coefficients		Standard coefficients	*t*	*p*
			B	*Standard Error*	*Beta*		
1	1	Constant	2.604	0.326	0.000	7.994	0.000
		Concentration on other positive aspects	–0.052	0.024	–0.243	–2.154	0.034
2	1	Constant	2.844	0.319	0.000	8.910	0.000
		Concentration on other positive aspects	–0.061	0.023	–0.302	–2.689	0.009
3	1	Constant	1.838	0.161	0.000	11.407	0.000
		Anxiety	0.058	0.019	0.393	3.057	0.004
4	1	Constant	1.724	0.316	0.000	5.452	0.000
		Depression	0.085	0.041	0.315	2.070	0.045
5	1	Constant	1.691	0.252	0.000	6.719	0.000
		Anxiety	0.066	0.028	0.584	2.387	0.036
	2	Constant	2.586	0.392	0.000	6.602	0.000
		Anxiety	0.084	0.023	0.744	3.625	0.005
		Acceptance	–0.067	0.025	–0.547	–2.665	0.024
6	1	Constant	0.598	0.316	0.000	1.894	0.091
		Catastrophising	0.175	0.030	0.893	5.937	0.000
FU	1	Constant	1.600	0.331	0.000	4.840	0.000
		Depression	0.107	0.047	0.312	2.279	0.027

Dependent variable: Cancer related fatigue (CRF) at visit (v)1, v2, v3, v4, v5, v6 & follow-up visit (FU); *df* — degrees of freedom; β — non-standardized coefficient; *p* — p-value; t — *t-Student statistics*

crucial to continue multicentre research to address an issues of psychological and medical aspects of clinical response to the chemotherapy and CRF designed for larger cancer patients' group.

Conclusions

High level of adaptive coping strategies and low level of non-adaptive ones are the predictors of CRF. Emotional state of NSCLC patients undergoing palliative chemotherapy is the significant factor characterising level of perceived fatigue. More often observed symptoms of depression and higher level of anxiety are the predictors of perceived CRF. Due to the size of the studied group the results of this study should be interpreted with caution and further research should be undertaken to verify these findings.

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