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The Close Link between Anxiety and Cluster Symptoms in Lung Cancer Patients during First-Line Chemotherapy

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Abstract

Background: Lung cancer (LC) patients report simultaneous incidence of physical and psychosocial symptoms defined cluster symptoms (CS). As among chemotherapy induced nausea and vomiting (CINV) predictors, anxiety is a modifiable factor. The aim of this study was to investigate the link between anxiety development and CS in stage IV LC patients during first-line chemotherapy.

Methods: This is an additional analysis using data from previously published WALCE survey. Several items (anxiety, lack of self-confidence, fatigue, lack of appetite, pain, somnolence, dyspnea, general status, lack of trust in treatments) were investigated at four timepoints (T0-T3) using a Numerical Rating Scale. Factor analyses were run and factor scores included (together with sex, age class and chemotherapy scheme) in multivariate logistic ordinal models at each time points in order to evaluate risk factors for anxiety.

Results: Factor analyses showed two latent factors composed by the same items at each evaluation: physical CS (fatigue, somnolence, dyspnea, lack of self-confidence) and psychological CS (lack of trust in treatments, general status, lack of appetite). Physical CS was associated with an increased pre-chemotherapy anxiety risk, while during chemotherapy, both physical and psychological CS seemed to exert an influence on anxiety development.

Conclusions: A close link between anxiety and CS in LC patients is evident. More attention should be paid to the detection of CS and anxiety in LC patients during first-line chemotherapy, in order to early detect high-risk patients and implement preventive actions.

Keywords: Anxiety; Lung cancer; Cluster symptoms; Chemotherapy; Numerical rating scale; Psychosocial symptoms; Nausea/vomiting

Introduction

Lung cancer (LC) remains the most common cause of cancer-related death, accounting for approximately 20% of the total cancer death worldwide [1]. Several trials [2-6] have shown that both physical and non-physical symptoms have a great importance in cancer patients, especially in LC. Furthermore, uncontrolled symptoms complicate patient care and, if poorly managed, can potentially affect both quality of life (QoL) and the number of hospital admissions. In particular, in LC patients, some symptoms are frequently reported with a simultaneous incidence and are thus defined cluster symptoms (CS).

CS are often associated with poor patient performance and remain a major issue throughout the course of cancer treatment and thereafter. There are at least two groups of CS: the first one includes fatigue, pain, and sleep disorders; the second one respiratory symptom, such as cough and dyspnea [7,8]. In recent years, the role of distress (including

depression and anxiety) in LC patients has undergone greater monitoring [9].

In addition to CS, chemotherapy induced nausea and vomiting (CINV) is also known to be extremely relevant in LC patients, especially at the advanced/metastatic setting. Several literature data confirmed the negative impact of CINV on quality of life (QoL) of these patients and its close relationship with physical and psychological symptoms [10,11]. Despite significant progresses in the prevention and control, CINV is still representing an unmet need in the oncology field and a common clinical issue, particularly among LC patients.

Several studies have investigated a variety of factors that could predict and anticipate the development of CINV: female gender [12-14], younger age [9,15], history of nausea/vomiting [16,17], the emetogenicity of the chemotherapy [7] and anxiety [18,19], have all emerged as potential inducers. We recently explored the role of anxiety as predictor of CINV using data from a survey conducted by the WALCE (Women Against LC in Europe) Onlus group on stage IV Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC) patients undergoing first-line chemotherapy. We showed that pre-chemotherapy anxiety in its mild, moderate and severe manifestations, as well as mild, moderate and severe anxiety experienced after the start of chemotherapy, exposed patients to a higher risk of anticipatory and acute/delayed CINV, respectively [19].

In addition to CINV [20,21], anxiety seems to be also linked to other symptoms. There is a growing body of literature that relates depression and anxiety with increased pain, fatigue and low performance status in cancer patients [22]. However, it is still unclear which are the factors that tend to increase an advanced cancer patient's risk of developing anxiety and/or depression and, to date, only few studies have looked at these factors across different advanced cancer populations [23,24]. The objective of the present study was to investigate the possible link between anxiety development and CS in advanced LC patients during first-line chemotherapy based on the data obtained from the previous survey [19].

Research Methodology

This study was an additional analysis using data from the previously published WALCE survey [19]. The survey was planned and conducted by WALCE Onlus, a European advocacy group devoted to LC patients and their families. Questionnaires were developed in agreement with a psychologist and advocates to evaluate the impact of CINV in LC patients during first-line chemotherapy. Furthermore, to improve patient understanding, the survey was planned based on the Edmonton Symptom Assessment System (ESAS) [25].

Participating centers were 11 Italian Oncologic Institutions collaborating with WALCE for awareness and patient support programs and having strong expertise on LC treatment. From August 2015 to February 2016, stage IV NSCLC and SCLC patients referring to these centers took part in the survey. Questionnaires were administered to patients at four consecutive evaluations (T0, T1, T2 and T3) during first-line chemotherapy, before chemotherapy administration. The timing was so organized: day 1 of the first cycle (T0, chemotherapy-naive patients), day 1 of the II cycle (T1), day 1 of the III cycle (T2), day 1 of the fourth cycle (T3). The survey was administered in day-hospital after the patient had breakfasted and taken his usual drugs. Questionnaires investigated 11 physical and psychological aspects (anxiety, mood, fatigue, appetite, nausea, vomiting, pain, drowsiness, dyspnea, general condition and trust in

treatments) by means of a Numerical Rating Scale (NRS) ranging from 0 to 10 (Appendix A). Information about patients' demographic characteristics, clinical features, antiemetic therapy and opiate and anxiolytic therapy were also collected. Also, patients were grouped depending on the consumption of anxiolytics and/or opioids at T0, and multivariate ordinal logistic models were separately run for the two subgroups (patients receiving anxiolytics and/or opioids and patients receiving neither anxiolytics nor opioids).

Statistical Analysis

Descriptive statistics were used to have an overview on patients' demographic and clinical characteristics, as well as on treatments. Qualitative variables were described in terms of frequencies and percentages, while quantitative variables were described in terms of mean value, standard deviation (SD), median, first and third quartiles (Q1 and Q3).

Presence of anxiety was defined as a rating greater than zero assigned to the respective item. In addition, anxiety level was defined as mild when the rating was included in the range 1-3, moderate when ranging from 4 to 7, and severe when comprised in the range from 8 to 10.

An explorative analysis was performed to assess for potential differences in the score distributions of the item's mood, fatigue, appetite, pain, drowsiness, dyspnea, general condition and trust in treatments depending on the presence or absence of anxiety. For each item, at each time point, t-tests were run on mean scores of anxious and non-anxious patients to understand whether differences were statistically significant.

Since the main objective of the study was the understanding of the factors that could exert a role in the development of anxiety and the number of items collected was high, before implementing multivariate analyses, factorial analyses were run at each time point. The choice of this statistical technique allowed the reduction in the number of parameters to be estimated avoiding them to be biased [26].

In fact, factor analysis assumes that covariations among the observed variables is due to the presence of one or more latent variables that exert directional influence on these observed variables; factors were searched among the item's mood, fatigue, appetite, pain, drowsiness, dyspnea, general condition and trust in treatments by means of factorial analysis separately at T0, T1, T2 and T3. A principal components analysis with varimax rotation was used and factors were extracted using Kaiser rule and Scree Test [27-29].

Items were included if they met two basic criteria: first, if they loaded > 0.30 on one of the factors, second, if their loading on the factor was positive. For each patient, the total scores for the factors were calculated by summing the scores on the constituent items. The so-obtained factor scores were included as covariates (together with sex, age class and chemotherapy scheme) in the multivariate logistic ordinal models run at T0, T1, T2 and T3 and evaluating the risk factors for each anxiety level, which was the dependent variable.

p-values lower than 0.05 were considered statistically significant. All the analyses were performed with SAS 9.4 software.

Results

188 patients completed the questionnaire at T0, 164 at T1, 138 at T2 and 101 at T3. Duly compiled questionnaires accounted for 99%.

Patients' characteristics are reported in Table 1. Presence of anxiety was defined as a rating greater than zero assigned to the respective item, with anxiety level defined as mild when the rating was included in the range 1-3, moderate when ranging from 4 to 7 and severe when comprised in the range from 8 to 10.

Total Number of Patients: 188			
Gender	N (%)		
Male	134 (71)		
Female	54 (29)		
Age (Mean: 64.6; SD: 8.4; Min: 41.0; Max: 83.0)	N (%)		
40-50	13 (7)		
50-60	32 (17)		
60-70	92 (49)		
>70	51 (27)		
Histological Form	N (%)		
Adenocarcinoma	114 (61)		
Squamous carcinoma	36 (19)		
Small cells carcinoma	30 (16)		
Poorly differentiated carcinoma	7 (4)		
Other	1 (0)		
Antiemetic Class			
Chemotherapy	5-HT3 antagonists+ NK1 antagonists	5-HT3 antagonists only	Other
	N (%)	N (%)	N (%)
Carboplatin based	11 (13)	74 (86)	1 (1)
Cisplatin based	82 (83)	13 (13)	4 (4)
Others	0	2 (67)	1 (33)

Table 1: Patients' characteristics at T0.

Proportions of patients experiencing anxiety were quite high at each time point, even if a specific time trend cannot be observed, neither in terms of anxiety presence/absence, nor in terms of anxiety degree, except for severe anxiety. Interestingly, the proportion of patients perceiving a severe level of anxiety decreased during chemotherapy cycles. On average, patients experiencing anxiety (mild, moderate and severe degree) accounted for about 90% of the study population (Figure 1).

The explorative analysis, aimed at identifying potential differences between anxious and non-anxious patients based on the scores assigned to the items, revealed that differences do exist. In general, the items whose mean scores showed the most marked differences at all the considered time points were mood and fatigue.

Besides this, it is worth noting that, while for the item's mood, pain, dyspnea and general condition, the magnitude of the difference in mean scores between anxious and non-anxious patients stayed constant, for the items fatigue, appetite, drowsiness and trust in treatments the difference increased when going from T0 to T3 (Table 2).

The factor analyses performed at T0, T1, T2 and T3 showed that underneath the considered items there were two latent factors whose characteristics were very well defined. In fact, the two factors resulted to be composed by the same items at all the considered time points. Factor 1 was composed by the items fatigue, drowsiness, dyspnea and mood, while factor 2 was composed by the items trust in treatments, general condition and appetite.

Despite the grouping process of the items gave similar and unidirectional results, the load of each item within the corresponding factor was different at the considered time points. At T0, thus before chemotherapy initiation, the items that explained the most the factor 1 were physical ones, and fatigue, while the items that explained the most the factor 2 were psychological ones, in particular trust in treatments.
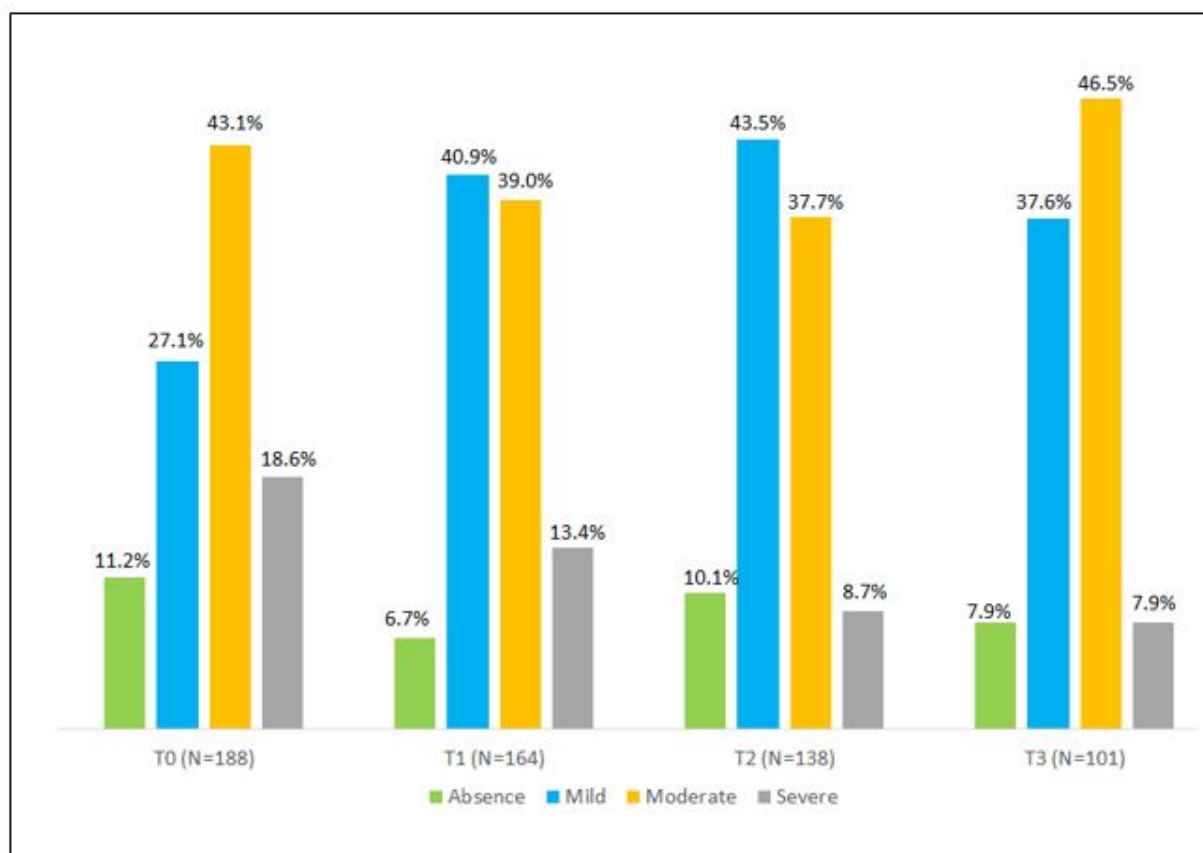
Figure 1: Patients with experience of anxiety (mild, moderate and severe degree) at T0, T1, T2 and T3.

At T1, results in terms of items loadings were comparable to those at T0, except for the item mood that ranked second; at T2 no differences were found with respect to T0. At T3, the item mood gained the second position within factor 1, while the items general condition and appetite gained the first and the second position within factor 2, respectively. As the item fatigue always ranked first within factor 1, and as most of the items that contribute to factor 1 were physical ones, factor 1 has been renamed into "physical symptoms" (physical CS). Similarly, as the items that ranked first at the different time points were trust in treatments and general condition, factor 2 has been renamed into "psychological symptoms" (psychological CS) (Table 3).

Variables		T0	T1	T2	T3
		Mean (SD); Q2 [Q1-Q3]			
Mood (0=I felt quite; 10=I felt insecure)					
Anxiety	No	0.10 (0.30); 0.00 [0.00 – 0.00] *	0.09 (0.30); 0.00 [0.00 – 0.00] *	0.71 (1.64); 0.00 [0.00 – 0.00] *	0.63 (1.06); 0.00 [0.00 – 1.00] *
	Yes	4.93 (2.49); 5.00 [3.00 – 7.00]	4.29 (2.45); 4.00 [2.00 – 6.00]	4.01 (2.10); 3.00 [2.00 – 5.00]	4.18 (2.33); 4.00 [2.00 – 6.00]
Fatigue (0=I had no feeling of fatigue; 10= I felt very weak)					
Anxiety	No	2.19 (2.68); 1.00 [0.00 – 3.00] *	2.09 (2.07); 2.00 [0.00 – 4.00] *	3.07 (3.00) 2.50 [0.00 – 6.00]	1.38 (2.00); 0.00 [0.00 – 3.00] *
	Yes	4.58 (2.92); 5.00 [2.00 – 7.00]	4.98 (2.51); 5.00 [3.00 – 7.00]	4.69 (2.42); 5.00 [3.00 – 7.00]	4.98 (2.65); 5.00 [3.00 – 7.00]

Appetite (0=I always feel hungry; 10= I have never felt hungry)					
Anxiety	No	2.67 (3.38); 1.00 [0.00 – 5.00]	2.45 (3.62); 0.00 [0.00 – 5.00]	2.07 (2.50); 0.50 [0.00 - 5.00] *	0.88 (0.99); 0.50 [0.00 – 2.00] *
	Yes	3.36 (2.52); 3.00 [1.00 – 5.00]	3.74 (2.36); 4.00 [2.00 – 5.50]	3.93 (2.58); 4.00 [2.00 – 6.00]	3.78 (2.33); 4.00 [2.00 – 5.00]
Pain (0=I have never had pain; 10= I always have pain)					
Anxiety	No	2.90 (3.60); 1.00 [0.00 – 5.00]	1.55 (2.50); 0.00 [0.00 – 2.00] *	1.71 (2.58); 0.00 [0.00 – 4.00]	1.00 (1.93); 0.00 [0.00 – 1.50] *
	Yes	3.98 (3.17); 4.00 [1.00 – 6.00]	3.57 (3.06); 3.00 [1.00 – 6.00]	2.91 (2.50); 3.00 [0.00 – 5.00]	3.31 (2.68); 3.00 [1.00 – 5.00]
Drowsiness (0=I have never had drowsiness; 10= I always have drowsiness)					
Anxiety	No	2.67 (3.29); 3.00 [1.00 – 4.00]	1.55 (2.16); 1.00 [0.00 – 3.00] *	2.86 (3.44); 1.50 [0.00 – 6.00]	0.75 (2.12); 0.00 [0.00 – 0.00] *
	Yes	3.50 (2.98); 3.00 [1.00 – 6.00]	3.98 (2.73); 4.00 [2.00 – 6.00]	3.75 (2.64); 3.00 [2.00 – 5.00]	3.82 (2.80); 3.00 [1.00 – 6.00]
Dyspnea (0=I Have never had shortness of dyspnea; 10= I always have shortness of dyspnea)					
Anxiety	No	1.86 (3.00); 0.00 [0.00 -3.00] *	1.09 (2.34); 0.00 [0.00 – 1.00] *	1.43 (2.21); 0.00 [0.00 – 2.00] *	0.50 (0.76); 0.00 [0.00 – 1.00] *
	Yes	3.28 (10.86); 2.00 [1.00 – 3.01]	2.84 (2.63); 2.00 [0.00 – 5.00]	2.95 (2.43); 3.00 [1.00 – 4.00]	3.00 (2.75); 2.00 [1.00 – 5.00]
General condition (0=Excellent; 10= Awful)					
Anxiety	No	2.95 (3.07); 2.00 [0.00 – 5.00]	2.64 (3.58); 1.00 [0.00 – 3.00]	2.86 (2.98); 2.50 [0.00 – 5.00]	1.50 (1.60); 1.00 [0.50 – 2.50] *
	Yes	3.87 (2.15); 4.00 [2.00 – 5.00]	3.82 (1.90); 4.00 [2.00 – 5.00]	4.05 (1.96); 4.00 [3.00 – 5.00]	3.71 (1.87); 3.00 [2.00 – 5.00]
Trust in treatments (0=Complete; 10= None)					
Anxiety	No	1.71 (3.10); 0.00 [0.00 – 2.00]	1.09 (2.98); 0.00 [0.00 – 1.00]	0.29 (0.61); 0.00 [0.00 – 0.00] *	0.63 (1.06); 0.00 [0.00 – 1.00]
	Yes	1.77 (2.12); 1.00 [0.00 – 3.00]	1.59 (1.91); 1.00 [0.00 – 2.00]	2.33 (2.37); 2.00 [0.00 – 4.00]	1.90 (1.89); 2.00 [0.00 – 3.00]
* p-value resulting from t-test is statistically significant.					

Table 2: Mean scores of the item's mood, fatigue, appetite, pain, drowsiness, dyspnea, general condition and trust in treatments stratified by anxiety presence/absence at T0, T1, T2 and T3.

Factors	Timing							
	T0		**T1**		**T2**		**T3**	
Physical symptoms (Physical CS)	Loading	Ranking	Loading	Ranking	Loading	Ranking	Loading	Ranking
Fatigue	0.76	1	0.79	1	0.87	1	0.87	1
Drowsiness	0.59	2	0.66	3	0.66	2	0.66	2

	Loading	Ranking	Loading	Ranking	Loading	Ranking	Loading	Ranking
Dyspnea	0.56	3	0.49		0.57	3	0.45	
Pain	0.47		0.49		0.32		0.46	
Mood	0.46		0.67	2	0.47		0.50	3
Psychological symptoms (Psychological CS)	**Loading**	**Ranking**	**Loading**	**Ranking**	**Loading**	**Ranking**	**Loading**	**Ranking**
Trust in treatments	0.78	1	0.93	1	0.80	1	0.61	3
General condition	0.60	2	0.55	2	0.67	2	0.69	1
Appetite	0.54	3	0.36	3	0.66	3	0.63	2
Eigenvalues	**Physical CS**		**Physical CS**		**Physical CS**		**Physical CS**	
	$\lambda=4.00$	$\lambda=7.31$		$\lambda=6.22$		$\lambda=5.46$		
	Psychological CS	**Psychological CS**		**Psychological CS**		**Psychological CS**		
	$\lambda=2.08$	$\lambda=4.17$		$\lambda=3.00$		$\lambda=2.05$		
	Physical CS	**Physical CS**		**Physical CS**		**Physical CS**		
	54%	36%		58%		66%		
Proportion of variance	**Psychological CS**		**Psychological CS**		**Psychological CS**		**Psychological CS**	
	46%	64%		42%		34%		

Table 3: Results from the factor analysis at T0, T1, T2 and T3.

Results from the multivariate ordinal logistic models showed that experiencing physical CS is associated with an increased risk of experiencing pre-chemotherapy anxiety, while no effect of psychological CS was detected before undergoing chemotherapy. Once chemotherapy has started, both physical and psychological CS seemed to exert an influence on anxiety development at T1, T2 and T3. None of all the other considered variables, except for gender at T3, seemed to be associated with anxiety occurrence (Table 4). Furthermore, the possible influence of anxiolytics and/or opioids was investigated. At T0, 55 patients used these drugs. Results from the subgroups analyses performed on patients receiving anxiolytics and/or opioids and on patients not receiving neither anxiolytics nor opioids did not differ from results on the total population (data not shown).

Covariates								
Gender	**T0**		**T1**		**T2**		**T3**	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Female versus male	1.81	0.94 – 3.49	0.78	0.37 – 1.63	1.19	0.56 – 2.51	3.23*	1.24 – 8.41
Age class								
50-60 versus 40-50	0.72	0.20 – 2.56	0.59	0.15 – 2.36	1.18	0.29 – 4.83	1.06	0.15 – 7.55
60-70 versus 40-50	0.89	0.28 – 2.87	0.41	0.11 – 1.46	1.29	0.35 – 4.81	1.33	0.21 – 8.36
70+ versus 40-50	0.52	0.15 – 1.82	0.36	0.09 – 1.46	1.27	0.30 – 5.35	1.42	0.19 – 10.87
Chemotherapy agent								
Cisplatin versus carboplatin	0.84	0.47 – 1.51	1.11	0.57 – 2.17	1.05	0.53 – 2.08	0.70	0.30 – 1.64
Physical CS	3.22*	2.22 – 4.65	8.06*	4.90 – 13.27	2.40*	1.63 – 3.55	4.19*	2.43 – 7.23
Psychological CS	1.27	0.92 – 1.77	1.48*	1.04 – 2.11	2.19*	1.47 – 3.28	2.50*	1.48 – 4.25

Table 4: Results from the multivariate ordinal logistic models run at T0, T1, T2 and T3.

Discussion

Five major findings emerged from the survey: 1) on average, the proportion of patients experiencing anxiety both before and after chemotherapy start was very high; 2) interestingly, proportions of patients with a severe level of anxiety decreased during chemotherapy cycles; 3) perception of the investigated items was worse in patients experiencing anxiety when compared to that of non-anxious patients; 4) the presence of physical symptoms was a strong predictor of pre-chemotherapy anxiety development; 5) the presence of both physical and psychological symptoms was a strong predictor of anxiety development after the first cycle of chemotherapy.

The description of anxiety among cancer patients is an established condition and its prevalence among cancer-affected patients is higher than in the general population [30]. In particular, an investigation on patient-reported distress associated with cancer diagnoses found that the prevalence of psychological distress varied by cancer type: LC patients experienced the highest levels of distress [31]. Carlsen and colleagues [32] showed that LC patients are at high risk for psychosocial problems during and after treatment and found out that one out of four people with LC experiences periods of depression or other psychosocial problems during their treatment. Similarly, a United Kingdom study found the prevalence of anxiety and depression to be 43% among patients with SCLC [33]. It has also been observed that anxiety increases during the course of the disease from baseline levels. In fact, the study by Montazeri [34] reported that, at the time of diagnosis, 16% of LC patients were anxious. After three months, the percentage almost doubled. In light of this, the elevated proportion of patients experiencing anxiety found by the present study is not surprising, in particular when considering that all the patients participating in the survey were at stage IV of the disease.

Another noteworthy result from this study is the observed decrease in the proportion of patients experiencing a severe level of anxiety from T0, before starting chemotherapy, to T3, before the start of the fourth chemotherapy cycle. A decrease in anxiety during chemotherapy cycles has been previously observed in a study by Bergerot [35] on hematological cancer patients. Similarly, to the present study, patients were asked to self-report their anxiety level at three time-points, i.e., before the start of first chemotherapy cycle, in the middle of treatment protocol and at the last day of chemotherapy treatment. Anxiety level was found to decrease. The authors concluded that the improvement in perceived anxiety could be interpreted as an indicator of the quality of cancer care provided. These conclusions are in line with the opinion of the authors of the present study. In fact, very high levels of trust in treatments have been here observed, with this probably due also to the fact that centers involved in the study collaborate with WALCE Onlus, thus they actively participate to awareness and patient support programs.

The worse perception of the investigated items detected among anxious patients when compared with non-anxious ones, confirms the existence of a strong relationships between anxiety and cancer-related symptoms, that is also well documented in the literature [36]. A study by Salvo [24] examined the contribution of several factors in the development of anxiety. Younger age, female gender, nausea, drowsiness, dyspnea and overall well-being resulted to be significantly associated with anxiety. A systematic review by Brown [37] focused on the association between cancer-related fatigue, depression and anxiety. Despite questioning whether cancer-related fatigue might be a cause, a consequence or the product of a common pathway of anxiety and depression, the authors concluded that anxiety is consistently associated with cancer-related fatigue. A recent study in fifty LC patients found a significant relationship between the presentation of anxiety and depression and the expression of some physical symptoms and wellbeing especially with fatigue [38]. Smith [39] evaluated relationships between QOL, dyspnea, trait anxiety in 120 outpatients with stage I-IV lung. Results showed that anxiety scores were statistically significantly higher in patients with higher levels of dyspnea.

A further important findings emerging from the present study is the key role of physical symptoms in the development of pre-chemotherapy anxiety, as well as the key role of both physical and psychological symptoms in the development of anxiety during the course of chemotherapy cycles. These results, and particularly the influence of physical symptoms on pre-chemotherapy anxiety, suggest that programs aimed at improving patients' functioning could also contribute in decreasing the level of perceived anxiety. In a study by Quist [40], LC patients with stage IIIB-IV NSCLC and SCLC extended disease, undergoing chemotherapy, participated to a physical training session. Several parameters, including lung capacity, aerobic capacity, functional capacity, muscle strength and anxiety were measured before and after the training. Both physical parameters, as well as anxiety level, improved after the training. Authors indicated as a possible explanation for the change in anxiety that the patients in this study significantly increased their aerobic capacity and functional capacity. Mustian and colleagues [41] suggested that to cope with stress and anxiety caused by changes in functioning from fatigue and other somatic symptoms, a variety of nonpharmacological interventions (e.g., exercise, stress management) may be beneficial for patients with cancer.

As stated in the previously published paper, a strong point of the present study was the homogeneity of the sample in terms of type of neoplasia, stage, chemotherapy line, treatment and adherence to guidelines. Furthermore, the proportion of duly compiled questionnaire was very high, probably reflecting the interest in the investigated issue and ensuring the accuracy of collected data [19].

There are two limitations of this study. The first is the use of a scale not perfectly validated for the measurement of anxiety. However, in the survey used the screening was based on a numerical scale as in the questionnaire ESAS. This feature could compensate this first limitation. In fact, Ripamonti [42] compared the ESAS with Hospital Anxiety Depression Scale (HADS) in a cross-sectional study was carried out on 194 patients with solid (108) or hematologic malignances. The results showed that ESAS anxiety or depression scores >3 detected quite well the severe depression HADS cases (Sensibility = 75, Specificity = 84; Sensibility = 87, Specificity = 90, respectively), concluding that anxiety or depression ESAS items score >3 can be applied as a useful in cancer patients.

The second limitation of the present study is represented by the fact that, indubitably, when evaluating anxiety and all the other physical and psychological symptoms here investigated, it is very difficult to understand deeply their cause-effect relationships. The conceptual model proposed by the authors considers anxiety as the dependent variable, thus, the one influenced by all the other items. However, this is a perspective, and further studies would be needed in order to confirm this hypothesis. Moreover, no matter which the adopted perspective is, what is becoming more and more clear and unquestionable is that an association between anxiety and cluster symptoms in LC patients does exist. Thus, healthcare professionals should be aware that acting on these symptoms could produce a

beneficial effect on anxiety, but also that acting on anxiety could improve cancer-related symptoms.

Finally, the close link between anxiety and CINV should not be forgotten. The identification of LC patients perceiving physical symptoms before chemotherapy initiation, together with tailored programs aimed at improving their functioning, could contribute in reducing anticipatory and acute CINV [19].

Conclusion

The analysis performed in this study showed a close link between anxiety and CS in patients with LC. A timely planning of tailored programs for LC patients should be foreseen as soon as a patient is referred to a cancer center. These programs should be based on a continuous dialogue between the patients and the healthcare professionals, who, once adequately trained, should be able to identify patients that are at risk of developing anxiety and, consequently, implement preventive actions.

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