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ORIGINAL PAPER

Anxiety and Depression in Non-Small Cell Lung Cancer Patients Receiving Chemotherapy Compared to Those Receiving Immunotherapy

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ABSTRACT

Background: *Non-small cell lung cancer (NSCLC) presents with a range of symptoms and is associated with a poor prognosis. Although both immunotherapy and chemotherapy improve survival, they are still associated with psychological disorders due to the reduced quality of life. This study aimed to investigate the levels of anxiety and depression in Greek patients with NSCLC receiving second-line chemotherapy compared to second-line immunotherapy.*

Materials and methods: *This is a comparative, prospective, non-randomized follow-up study in which measurement scales have been used to compare data from NSCLC patients in two hospitals in Athens, Greece. All patients completed a demographic data form in the first therapy cycle, while the hospital anxiety and depression scale (HADS) (value range 0-21) was completed from treatment cycle 1 to treatment cycle 6.*

Results: *Of the 111 selected patients, the majority (75.7%) were men, with a mean age of 66.5±9.2 years. Second-line chemotherapy was received by 61 patients and second-line immunotherapy by 50 patients. According to HADS, from treatment cycle 1 to treatment cycle 6, the mean anxiety score decreased from 4.83±5.1 to 3.2±3.8 ($p=0.287$), while the mean depression score decreased from 5.64±5.53 to 4.61±4.75 ($p=0.113$). Depressive symptoms were statistically significantly higher in patients who received chemotherapy from the fourth cycle onwards ($p<0.05$), but in any of the study groups, the value did not exceed the critical*

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threshold of seven points. In the anxiety subscale, after cycle 3 there was a significant decrease (p=0.014) of a similar degree (p=0.608) in both groups.

Conclusions: *The present study was the first attempt to investigate differences in psychological symptoms between treatment groups in Greek NSCLC patients. Anxiety and depression levels did not appear to be serious problems in the chemotherapy and immunotherapy group of patients.*

Keywords: anxiety, chemotherapy, depression, immunotherapy, non-small cell lung cancer, psychological symptoms.

INTRODUCTION

Lung cancer is one of the most common types of cancer worldwide and the leading cause of cancer death in both men and women. It is classified in two main histological types: non-small cell lung cancer (NSCLC), which accounts for 85%–90% of cases, and small cell lung cancer, which accounts for 10%–15% of cases (1).

Lung cancer patients experience higher levels of depression (21%–44%) compared to patients with other types of cancer (7%–23%) (2). Moments of transient stress are to be expected, but one study found that 43.5% of people with lung cancer experienced stress levels high enough to reduce their quality of life (3) due to the significant burden of co-morbidities and symptoms compared to the general population or survivors with other cancer types (4-6).

Living with lung cancer can lead to psychological disorders in many ways and at any stage of the disease. The knowledge and perceptions about cancer, the symptoms of the disease, the prescribed treatments and the toxicity of drugs significantly influence the patients' perceptions of their health status and life in general (7). Furthermore, cancer diagnosis, serious physical health condition and treatment can affect mental health, leading to sadness or even thoughts and feelings of hopelessness. Depression is much more likely to occur when the affected persons have more symptoms and when lung cancer negatively impacts their daily activities (8). The stigma of the disease and its reputation as a cancer with a relatively poor prognosis can add further anxiety to a journey already filled with potential triggers for anxiety. Anxiety triggers can range from the uncertainty of treatment to the fear of losing independence and death. Persistent anxiety or anxiety that is out of proportion can have a significant effect on daily life, interfering with treatment (3).

Although treatments such as chemotherapy or immunotherapy improve survival, they continue to be associated with psychological disorders due to their toxicity and effect on patients' quality of life (3, 9-12). Research gaps still exist in assessing psychological symptoms over time in NSCLC populations, depending on the type of treatment they receive.

The present comparative, prospective, non-randomized follow-up study aimed to investigate the anxiety and depression levels in NSCLC patients receiving second-line chemotherapy compared to those receiving second-line immunotherapy. ❑

MATERIALS AND METHODS

The sample consisted of all patients with NSCLC undergoing second-line chemotherapy or immunotherapy in two one-day clinics in Athens, Greece, between January 2020 and December 2021. The following selection criteria were used: age >18 years, documented diagnosis of NSCLC, receiving only second-line chemotherapy or immunotherapy, ability to communicate in Greek and satisfactory cognitive function.

Out of 125 patients who met the inclusion criteria, 14 refused to participate in the study (response rate 88.8%). Therefore, the remaining 111 patients were finally included in our two study groups, with 61 participants receiving docetaxel or pemetrexed (the second-line chemotherapy group) and 50 subjects receiving nivolumab or pembrolizumab (the second-line immunotherapy group).

Demographic characteristics were obtained from the patients, while clinical data related to disease and treatment were extracted from their medical records. The TNM staging system was

used to describe the size and extent of lung cancer (13). The Eastern Cooperative Oncology Group (ECOG) scale was applied, classifying patients according to their functional impairment – scores from 0 to 4. A score of 0 represents the patient condition of being able to perform all activities without limitations, while a score of four represents the patient who is completely unable to do anything or take care of oneself. As the degree of the scale increases, so does the disorder of the patient's functionality (14). To assess psychological symptoms HADS, a 14-parameter assessment tool, was used after obtaining the relevant permission. The scale consists of seven questions relating to anxiety (anxiety subscale) and seven questions concerning depression (depression subscale). The questions are answered on a four-point Likert scale, from 0 (not at all) to 3 (it happens to me all the time or often). Each subscale outputs a total score as the sum of the scores of each question and its range varies from 0 to 21. Scores from 0-7 are considered normal levels of anxiety and depression (a non-pathological condition). A score of 8-10 reflects intermediate situations and depicts a borderline problem (a doubtful case). A score of 11-21 corresponds to a severe problem that requires appropriate treatment (a pathological condition). These cutoff points apply to both the anxiety and depression subscales and help to categorize their severity, aiding clinicians in diagnosing and planning interventions (15). The HADS is validated in Greek by Mystakidou *et al* and shows adequate internal consistency after use in Greek patients with advanced cancer (16). Patients included in the present study were assessed at six different time points during the first cycle of second-line treatment and at each subsequent treatment cycle.

Ethical issues

Our study was conducted according to the guidelines of the Declaration of Helsinki (17). The hospitals' scientific committees approved the study protocol and all participating patients signed a consent form.

Statistical analysis

Means and standard deviations (SD) were used to describe the quantitative variables. Absolute (N) and relative (%) frequencies were used to describe qualitative variables. To compare proportions, Pearson's χ^2 test or Fisher's exact test was used, where necessary. The Student's t-test or the non-parametric Mann-Whitney test was used to compare quantitative variables between two groups. Mixed-linear models were used to test for differences in measurements over time. Also, the above method assessed whether the degree of change over time was different between the two groups. Mixed linear models were made using logarithmic transformations if the scale was not normally distributed. Significance levels are two-sided, and statistical significance was set at 0.05. The statistical programs SPSS 26.0 and STATA 11.0 were used for the analysis. ❑

RESULTS

At the beginning of the study, the 111 patients with NSCLC had a mean age of 66.5±9.2 years. The demographic characteristics, including gender, age, profession, marital status, income and education, were similar between the 61 patients who received chemotherapy and the 50 ones who received immunotherapy (p>0.05) (Table 1).

TABLE 1. Demographic characteristics of patients by type of treatment

	Type of second-line therapy		
	Chemotherapy (N=61)	**Immunotherapy (N=50)**	**P**
Gender, male	44 (72.1%)	40 (80%)	0.336+
Age, years (mean, SD)	67 (10.1)	66 (8.2)	0.593‡
Profession			0.890++
State employee	5 (8.2%)	3 (6%)	
Private employee	9 (14.8%)	10 (20%)	
Unemployed	3 (4.9%)	1 (2%)	
Retired	41 (67.2%)	34 (68%)	
Household	3 (4.9%)	2 (4%)	
Marital status			0.059++
Singles	6 (9.8%)	0 (0%)	
Married	36 (59%)	34 (68%)	
Widowers	15 (24.6%)	9 (18%)	
Divorced	4 (6.6%)	7 (14%)	
Children, yes	48 (78.7%)	45 (90%)	0.108+
Monthly income			0.199++
<€1000	22 (36,1%)	11 (22%)	
€1001 – €1500	24 (39,3%)	25 (50%)	
€1501 – €2000	13 (21,3%)	14 (28%)	
€2001 – €4000	2 (3,3%)	0 (0%)	
Education			0.580++
Primary school	28 (45.9%)	29 (58%)	
High school	17 (27.9%)	11 (22%)	
University	11 (18%)	9 (18%)	
Postgraduate studies	5 (8.2%)	1 (2%)	

SD = standard deviation; +Pearson's χ^2 test; ++Fisher's exact test; ‡Student's t-test

TABLE 2. Clinical characteristics of non-small cell lung cancer (NSCLC) patients by type of treatment

	Type of second-line therapy		
	Chemotherapy (N=61)	Immunotherapy (N=50)	P
Years since NSCLC diagnosis			0.211+
2	11 (18%)	14 (28%)	
3	50 (82%)	36 (72%)	
Disease stage			0.499++
2	1 (1.6%)	0 (0%)	
3	24 (39.3%)	24 (48%)	
4	36 (59%)	26 (52%)	
Tumor			0.831+
2	3 (4.9%)	3 (6%)	
3	18 (29.5%)	17 (34%)	
4	40 (65.6%)	30 (60%)	
Nodes			**0.010+**
0	0 (0%)	1 (2%)	
1	7 (11.5%)	3 (6%)	
2	20 (32.8%)	31 (62%)	
3	34 (55.7%)	15 (30%)	
Metastasis, yes	51 (83.6%)	34 (68%)	**0.050+**
Metastatic site			
Brain	23 (45.1%)	3 (8.8%)	**<0.001+**
Bone	14 (27.5%)	9 (26.5%)	0.921+
Liver	15 (29.4%)	10 (29.4%)	>0.999+
Adrenal glands	28 (54.9%)	16 (47.1%)	0.478+
Lungs	20 (39.2%)	14 (41.2%)	0.857+
Co-morbidities			0.342++
Hypertension	33 (54.1%)	22 (44%)	0.538++
Diabetes mellitus	17 (27.9%)	17 (34%)	0.105++
Hyperlipidemia	17 (27.9%)	7 (14%)	**0.018++**
Atrial fibrillation	7 (11.5%)	15 (30%)	0.769++
COPD	8 (13.1%)	5 (10%)	

+Pearson's χ^2 test; ++Fisher's exact test; COPD = chronic obstructive pulmonary disease

Patients who underwent second-line chemotherapy had metastasis at a significantly higher rate compared to those who received second-line immunotherapy (83.6% *versus* 68%, p=0.05). Moreover, the number of patients with brain metastasis was significantly higher in the chemotherapy group compared to the immunotherapy group (45.1% *versus* 8.8%, p<0.001). The most common co-morbidity reported in both groups of patients was hypertension, followed by diabetes. The incidence rates of co-morbidities did not significantly differ between the two groups, except for atrial fibrillation, which was considerably higher among patients with immunotherapy (30% *versus* 11.5%, p=0.018) (Table 2).

Patient outcomes significantly differed between the two groups. The relapse rate was higher in subjects who received chemotherapy (55.7%) compared to those who were given immunotherapy (26%, p=0.006). The mean time to relapse was 137.5 days (SD=21.5 days) for patients who received chemotherapy and 133.7 days (SD=19.4 days) for those who underwent immunotherapy. The rate of death was greater in the chemotherapy group (26.2%) compared to the immunotherapy one (6%, p=0.005), with the mean time to death being identical in the two groups (161.9 days).

TABLE 3. Functionality assessment according to the Eastern Cooperative Oncology Group (ECOG)

	ECOG scale score (mean, SD)		
	Chemotherapy group (N=61)	Immunotherapy group (N=50)	P+
Treatment cycle			
1	0.7 (0.94)	0.68 (0.84)	0.934
2	0.89 (1.16)	0.84 (1.06)	0.959
3	1.08 (1.33)	0.9 (1.11)	0.600
4	1 (1.21)	0.73 (0.99)	0.409
5	0.86 (1.14)	0.76 (0.94)	0.882
6	0.63 (0.93)	0.62 (0.92)	0.994

SD = standard deviation; +Mann-Whitney test

TABLE 4. Psychological symptoms according to the hospital anxiety and depression scale

	Depression subscale (mean, SD)		
	All patients (N=111)		P+
Treatment cycle			0.113
1	5.64 (5.53)		
6	4.61 (4.75)		
	Chemotherapy group (N=61)	Immunotherapy group (N=50)	P+
Treatment cycle			
1	5.69 (5.33)	5.58 (5.83)	0.707
2	6.49 (6.08)	5.64 (5.79)	0.376
3	7.49 (6.22)	5.72 (5.84)	0.08
4	7.04 (5.3)	4.82 (5.51)	**0.02**
5	6.74 (5.98)	4.07 (4.83)	**0.027**
6	6.33 (5.02)	3.35 (4.18)	**0.025**
	Anxiety subscale (mean, SD)		
	All patients (N=111)		P+
Treatment cycle			0.287
1	4.83 (5.1)		
6	3.2 (3.8)		
	Chemotherapy group (N=61)	Immunotherapy group (N=50)	P+
Treatment cycle			
1	4.23 (4.62)	5.56 (5.58)	0.341
2	4.98 (4.97)	5.58 (5.85)	0.821
3	5.39 (5.29)	5.86 (6.31)	0.971
4	4.71 (4.44)	4.56 (5.02)	0.491
5	4.2 (4.36)	3.63 (4.33)	0.38
6	2.89 (3.52)	3.41 (4.02)	0.749

SD = standard deviation; +Mann-Whitney test

In every treatment cycle, the two groups' ECOG scale scores were comparable (p>0.05). Furthermore, none of the groups' functionality changed during the treatment cycles (Table 3).

According to HADS, the mean anxiety score decreased from 4.83 (±5.1) in treatment cycle 1 to 3.2 (±3.8) in treatment cycle 6 (p=0.287), while the mean depression score decreased from 5.64 (±5.53) in treatment cycle 1 to 4.61 (±4.75) in treatment cycle 6 (p=0.113).

Depressive symptoms were similar in the two groups of patients during the first three treatment cycles. However, during cycles 4, 5 and 6, depressive symptoms were significantly higher in patients who received chemotherapy. The depression score did not change significantly over time in either group (β=-0.001, SE=0.001, p=0.652). The anxiety score was similar in the two groups of patients in all treatment cycles, indicating a similar level of anxiety. Anxiety scores up to cycle 3 did not change significantly in either group (β=0.004, SE=0.004, p=0.240), while after cycle 3 there was a significant decrease (β=-0.003, SE=0.003, p=0.014) of a similar degree (β=0.003, SE=0.006, p=0.608) in both groups (Table 4). ❑

DISCUSSION

Oncology health professionals often face the problem to distinguish normal psychological responses to cancer disease from symptoms of psychiatric disorders. Cancer patients experience psychological distress during or after treatment (18, 19). However, depression and anxiety are sometimes underestimated, underdiagnosed and undertreated even when they appear in their most severe forms, due to overlapping symptoms with cancer-related fatigue and pain (20). Furthermore, only a minority of detected cases are referred for further help or offered psychotherapy (21, 22). In a study of 472 low-income women with breast or gynecological cancer, it was found that 12% of patients with major depression were prescribed antidepressants and only 5% received psychotherapy (23). The under-detection of psychiatric disorders also seems to be linked to the workload pressure experienced by oncology professionals (24). Also, this may be because anxiety can be difficult to separate from adjustment disorders and is often co-occurring with depression (24).

Depression and anxiety among cancer patients appear to be associated with higher healthcare costs (25, 26) and lower cancer treatment adherence (27, 28). A retrospective data analysis of 5055 cancer patients in the USA reported that depressed patients have significantly more annual healthcare visits, emergency department visits and hospital readmissions compared to non-depressed cancer patients (25). In addition, depression and anxiety can significantly affect a patient's comfort, quality of life and ability to make appropriate treatment decisions, negatively affecting survival (19, 29, 30).

In the present study, anxiety and depression seem to be not severe problems in NSCLC patients since, in all treatment cycles, the score of both subscales does not exceed seven points, which is the upper limit for non-pathological conditions. Depression and anxiety levels in lung cancer patients vary between different countries, ranging between 32.4% and 100%, while the frequency of anxiety ranges between 30% and 97.2% (31-34). In Greece, a recent study by Pra-

pa *et al* showed that 35.6% and 40% of 135 lung cancer patients reported depressive or anxiety symptoms, respectively (35).

From our results, it appeared that depressive symptoms were statistically significantly higher in patients who received chemotherapy compared to those who underwent immunotherapy from the fourth cycle onwards ($p<0.05$). Nevertheless, in all groups the subscale score did not reach eight points, which represents a borderline depression problem. This may be because psychological symptoms tend to decrease as time passes since diagnosis and health perceptions improve, highlighting the resilience of cancer patients over time, in contrast to those who are first diagnosed (36). Also, oncology health professionals may gradually extend their thorough interventions in other unmet health (psychological, social, etc) needs.

Furthermore, there was no statistically significant change over time in depression subscale values in either patient group ($p>0.05$). On the contrary, in the anxiety subscale, the score was similar in all patients (less than eight points), regardless of the treatment group, while a decrease was noted in both groups from the third cycle onwards. Our findings are confirmed by McFarland's study, which reports that immunotherapy is associated with a lower incidence of depression compared to chemotherapy ($p=0.04$) in lung cancer patients when the two groups do not differ in age, gender or baseline functional status (37).

Our study partially confirms that anxiety and depression may have a different course from diagnosis to the end of treatment. Anxiety tends to reflect an expected reaction to diagnosis and is often transient, whereas depression is more likely to reflect a stable state (38). The study by Linden *et al* is the first to provide representative data on anxiety and depressive symptoms concurrently with the course of the disease (39). Approximately 19% and 13% of patients reached the cutoff for a level of anxiety or depression, respectively. Also, it is interesting that the levels of anxiety and depression vary significantly depending on the type of cancer, gender and age. This means that separate risk groups cover a full spectrum (39). In the same study, a clear inverse relationship between emotional distress and age was observed. The prevalence rates of anxiety and depression were higher in the younger age group and lower in older adults. This is likely due to the greater disruption of daily life in younger cancer patients, whereas older patients may already have impairments in everyday functioning and therefore, they are better prepared, both mentally and emotionally, to accept the disease. However, for some types of cancer, there does not appear to be an effect of age, suggesting that cancers with a poor prognosis, such as lung cancer, affect all age groups equally (39).

There is a growing body of evidence linking various indications of mental disorders, including diagnoses of depression and anxiety disorders, with problems such as pain, weakness or fatigue and low functioning (40). Some of these studies included patients treated for advanced disease. As noted by Hotopf *et al*, the study of mental disorders in palliative care was characterized by small samples, a lack of structured diagnostic interviews and little focus on the issue of co-morbidity (41). In this context, the impact of mental disorders on other dimensions of quality of life remains unclear. This issue is crucial because it has been suggested that mental disorders may make the physical symptoms of advanced disease more difficult to manage. They may also affect patients' social or existential well-being in this critical phase of their lives (40). Furthermore, the intensity of depressive symptoms is associated with a loss of functioning (8).

Studies of the treatment of depression and anxiety in cancer patients show that there is no agreement regarding the initiation of antidepressants, which are effective for both categories of disorders. These discrepancies make it difficult to make recommendations that would lead to improved screening practices and better access to care for patients with depression and/or anxiety disorders. Of course, there may be other reasons for deciding not to start antidepressant treatment (40). For example, if distress arises from existential concerns, then psychological or spiritual interventions may be considered more appropriate (42). Also, some patients may refuse to take medications, or there may be medical concerns about side effects and drug interactions. However, existing studies highlight the need for continued vigilance in the diagnostic assessment of depression and anxiety disorders in cancer patients. There also needs to be greater agreement on when and in which patients to start treatment, as anxiety and depression disor-

ders are associated with poor quality of life in people who are dying from cancer (40).

Some limitations of the present study should be considered when interpreting the results. The small sample size might reduce the statistical power, which is often observed in non-multicenter studies. Furthermore, due to the non-random sampling, it is difficult to generalize the study's findings, as non-randomization does not rule out the possibility that factors other than treatment may be related to the incidence of anxiety and depression. ❑

CONCLUSIONS

In conclusion, our study findings demonstrated normal levels of anxiety and depression in both NSCLC patients receiving chemotherapy and those receiving immunotherapy. After the fourth cycle, depressive symptoms were higher in patients receiving chemotherapy, while anxiety symptoms decreased after the third cycle in both groups. Our results emphasize the need for multicenter studies to evaluate the prevalence of psychological symptoms in larger populations of patients with NSCLC, highlighting that therapeutic success should be determined not only by efficacy and prolongation of survival but also by self-reported quality of life. ❑

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