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Article

Quality of Life and Symptom Burden in Non-Small Cell Lung Cancer Patients Receiving Second-Line Chemotherapy Compared with Immunotherapy

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Abstract: *Background and Objectives:* The burdened symptomatology accompanying advanced non-small cell lung cancer (NSCLC) is associated with poor prognosis and lower quality of life (QoL). Although both chemotherapy and immunotherapy increase survival, they are still associated with reduced functionality due to their toxicity. This study aimed to estimate the QoL and symptom burden of NSCLC patients receiving second-line chemotherapy compared to patients receiving second-line immunotherapy. *Materials and Methods:* This comparative, prospective study, conducted from January 2020 to December 2021, included 111 NSCLC patients who were divided into two groups: 61 patients receiving second-line chemotherapy and 50 patients receiving second-line immunotherapy. Patients QoL and symptom burden were estimated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C-30) (value range 0 - 100) from treatment cycle 1 to 6. *Results:* The QoL (mean score > 50) and functionality dimensions (mean score > 50) were moderate to good in both treatment groups, while the symptoms burden did not appear to be a serious problem (mean score < 50). From cycle 3 to cycle 5, the QoL was significantly better in the immunotherapy group. From cycle 3, role and social functioning scores were higher in the immunotherapy group, while emotional and cognitive functioning were higher from cycle 2 ($p < 0.05$). The chemotherapy group experienced higher levels of nausea/vomiting, constipation and financial difficulties in all cycles ($p < 0.05$). Fatigue and appetite loss were significantly greater from cycle 2 and insomnia was significantly greater from cycle 3. On the contrary, the immunotherapy group experienced higher levels of diarrhea in cycles 5 and 6 ($p < 0.05$). *Conclusions:* Although both therapy groups did not report significantly impaired QoL and severe symptoms, it seems that QoL improved in the immunotherapy group, which reported less symptom burden compared to the chemotherapy group.

Keywords: chemotherapy; immunotherapy; non-small cell lung cancer; symptoms; quality of life

1. Introduction

Non-small cell lung cancer (NSCLC), often diagnosed as advanced or metastatic disease, does not have a high survival rate, remaining one of the leading causes of cancer-related deaths among men and women. Progression-free survival often remains unsatisfactory and, furthermore, patients are generally symptomatic and clinically vulnerable [1]. Patients can experience symptoms specific to their disease process (such as cough or dyspnea) or more generalized symptoms (such as fatigue and loss of appetite) [2].

Given the incurable nature of metastatic NSCLC, the goals of oncology healthcare professionals should not only focus on controlling the disease, but it should also be directed at optimizing the patient's quality of life (QoL). Health-related QoL (HRQoL) is a multi-dimensional concept that addresses the functional effect of a health status and/or the patient's treatment. It refers to physical, role, emotional, social, cognitive, sexual and spiritual functioning on individual levels [3–5]. HRQoL data is a core element for treatment comparisons, supports daily clinical treatment decision-making, improves communication between patients and clinicians and facilitates clinical and economic evaluations to define the most efficient allocation of healthcare resources [6]. Patient-reported HRQoL data aids clinicians to understand better toxicity and symptoms experienced by patients, as subjective symptoms, such as fatigue and pain are frequently under-reported [7].

Chemotherapy seems to improve QoL when compared to best supportive care, likely due to better overall physical functioning and alleviation of disease-related symptoms [8]. However, the administration of subsequent lines of chemotherapy after the progression of the disease has been associated with worse outcomes with regards to physical conditioning and symptom burden [9]. Despite efforts to maximize QoL, patients unfortunately suffer a significant amount of therapy-related adverse effects as a consequence of their treatment regimen. In recent years, immunotherapy has proven to be an effective treatment for patients with NSCLC, outperforming chemotherapy in terms of response rate, overall survival, progression-free survival, and safety [10–18].

Although it is commonly assumed that a lower frequency of adverse events equates to a better overall QoL, few studies have examined its change over time in NSCLC patients, depending on treatment type. Patients with advanced or metastatic NSCLC will likely be on treatment for the rest of their lives, and therefore the impact of disease-related symptoms and treatment-related side effects should be accounted for when evaluating HRQoL. Understanding the patient experience of disease symptoms and treatment-related adverse events is important in improving clinical outcomes and HRQoL [10–18].

This comparative, prospective, non-randomized follow-up study aimed to estimate the QoL and symptom burden of NSCLC patients receiving second-line chemotherapy compared to patients receiving second-line immunotherapy.

2. Materials and Methods

2.1. Patient Population

The sample consisted of all patients with NSCLC undergoing second-line chemotherapy or immunotherapy in one-day clinics of two hospitals in Athens between January 2020 and December 2021. The inclusion criteria were patients of both genders, male or female subjects over 18, with a documented NSCLC diagnosis, receiving only second-line chemotherapy or second-line immunotherapy, being able to communicate in Greek, and having adequate cognitive function.

The exclusion criteria included receiving chemotherapy and immunotherapy in combination, as well as having a recognized mental health issue.

Out of 125 patients who met the inclusion criteria, 14 refused to participate (response rate 88.8%), mainly due to lack of time. Finally, 111 patients participated: 61 patients in the second-line chemotherapy group and 50 in the second-line immunotherapy group. The first group received docetaxel or pemetrexed, while the second group received nivolumab or pembrolizumab. Demographic characteristics and clinical data related to disease and treatment were obtained from patients and their medical records.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the two hospitals' Ethics Committees. Written informed consent was obtained from all the patients before their participation in this study.

2.2. Quality of Life and Symptom Burden Assessment

To assess the QoL and symptom burden, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C-30), version 3.0 [19], was used after

obtaining the relevant permission. The questionnaire was validated in the Greek language [20] and completed by the patients. It consists of 30 questions and includes functioning (physical, role, emotional, cognitive and social), symptoms (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties) and global health/total QoL scales. The results of each scale are presented with a range of values from 0 to 100. Higher functioning and global health/total QoL scale values represent a higher level of functioning and QoL, respectively, while high ratings on symptom scale represent greater distress from the symptoms/problems.

Patients included in the study were assessed at six different time periods, during the first cycle of second-line therapy, and at each of the six following cycles.

2.3. 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. Significance levels were 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.

3. Results

Table 1 provides the baseline demographic and clinical variables of patients with NSCLC. This study included 111 patients, 61 of them (17 females and 44 males) receiving second-line chemotherapy and 50 of them (10 females and 40 males) receiving second-line immunotherapy, with a mean age of 67 ± 10.1 and 66 ± 8.2 , respectively. There was no statistically significant difference between the groups regarding their age, gender, marital status, education level and income status. Also, the two groups did not differ in terms of clinical characteristics, such as years since NSCLC diagnosis, disease stage, and previous radiotherapy or surgical resection. However, there were significantly more patients with metastases in the chemotherapy group, compared to the immunotherapy group ($p = 0.050$) (Table 1).

Table 1. Sample characteristics and differences between patients receiving second-line chemotherapy and immunotherapy.

Data	All patients (N=111)	Chemotherapy group (N=61)	Immunotherapy group (N=50)	P+
Gender, males	84 (75.7%)	44 (72.1%)	40 (80%)	0.336
Age, years (mean, SD)	66.5 (9.2)	67 (10.1)	66 (8.2)	0.593
Marital status				
Single	6 (5.4%)	6 (9.8%)	0 (0%)	0.059
Married	70 (63.1%)	36 (59%)	34 (68%)	
Divorced	11 (9.9%)	4 (6.6%)	7 (14%)	
Widow/widower	24 (21.6%)	15 (24.6%)	9 (18%)	
Educational level				
Primary school	57 (51.4%)	28 (45.9%)	29 (58%)	0.580
High school	28 (25.2%)	17 (27.9%)	11 (22%)	
University	26 (23.4%)	16 (26.2%)	10 (20%)	
Income status				
Bad/poor	33 (29.7%)	22 (36.1%)	11 (22%)	0.199
Adequate	49 (44.1%)	24 (39.3%)	25 (50%)	
Good	29 (26.1%)	15 (24.6%)	14 (28%)	
Years since diagnosis				
2	25 (22.5%)	11 (18%)	14 (28%)	0.211
3	86 (77.5%)	50 (82%)	36 (72%)	
Disease stage				
2	1 (0.9%)	1 (1.6%)	0 (0%)	0.499

3	48 (43.2%)	24 (39.3%)	24 (48%)	
4	62 (55.9%)	36 (59%)	26 (52%)	
Metastases	85 (76.6%)	51 (83.6%)	34 (68%)	0.050
Previous radiotherapy	83 (74.8%)	42 (68.9%)	41 (82%)	0.113
Previous surgical resection	47 (42.3%)	27 (44.3%)	20 (40%)	0.651

+chemotherapy vs. immunotherapy; SD = Standard Deviation.

According to the EORTC QLQ-C30 scale the mean value of the global health status/total QoL was above 50 points for all patients in all treatment cycles. Data regarding global health/total QoL differences between the two groups are presented in Table 2. In cycles 1 and 2 there were no significant differences in the QoL score between patients receiving chemotherapy and those receiving immunotherapy. The QoL was significantly better in the immunotherapy patients from treatment cycle 3 (mean difference 18 points) to treatment cycle 5 (mean difference 18.8 points), while in cycle 6 it was similar in both groups.

Table 2. Global health/total quality of life differences between therapy groups.

Treatment cycle	Global health/Total QoL (mean, SD) Range 0-100			
	Chemotherapy group (N=61)	Immunotherapy group (N=50)	Between groups difference	P
1	68.6 (28.4)	77.7 (31.2)	-9.1	0.111
2	63.4 (31.3)	74.8 (34.7)	-11.4	0.071
3	56.8 (33.8)	74.8 (35.7)	-18.0	0.008
4	63.0 (28.9)	79.8 (29.6)	-16.8	0.007
5	63.3 (32.4)	82.1 (27.0)	-18.8	0.007
6	75.6 (25)	86.5 (25.4)	-10.9	0.094

QoL = Quality of Life; SD = Standard Deviation.

According to the EORTC QLQ-C30 scale all functioning dimensions were above 50 points for all patients in all treatment cycles. The highest mean score was recorded in cognitive functioning (92.2 ± 15.1), followed by emotional (85.5 ± 17.2), physical (72.6 ± 27.5), social (69.7 ± 32.6) and role (66.1 ± 34.3) functioning. Table 3 presents data regarding functional scale score differences between the two groups. In cycle 1, there were no significant differences in functional scales scores between patients receiving chemotherapy and patients receiving immunotherapy. Physical functioning was similar in the two groups of patients throughout the treatment cycles. Role functioning score, as well as social functioning score, were significantly higher in patients receiving immunotherapy from cycle 3 onwards, while emotional and cognitive functioning scores were significantly higher in patients receiving immunotherapy from cycle 2 onwards.

Table 3. Functional scales score differences between therapy groups.

		Treatment cycles					
Functional scales (mean, SD) Range 0-100	Treatment groups	1	2	3	4	5	6
Physical functioning	CMT (N=61)	75.5 (24.9)	68.0 (29.4)	62.4 (33.4)	65.6 (27.4)	68.4 (29.6)	72.6 (25.8)
	IMT (N=50)	77.1 (25.1)	71.6 (29.7)	72.4 (30.5)	75.9 (28.3)	79.8 (23.1)	82.2 (22.9)
	P	0.746	0.522	0.105	0.085	0.062	0.123
Role functioning	CMT (N=61)	66.1 (35.7)	58.2 (36.6)	52.2 (37.9)	57.8 (36.7)	60.0 (37.1)	63.0 (34.1)
	IMT (N=50)	71.4 (32.6)	68.0 (36.2)	67.3 (37)	73.3 (32.1)	76.8 (28.6)	79.7 (28.1)
	P	0.423	0.161	0.037	0.035	0.029	0.035
Emotional functioning	CMT (N=61)	81.7 (20.0)	79.9 (20.8)	77.8 (22.0)	80.8 (18.7)	81.7 (20.5)	82.8 (21.5)
	IMT (N=50)	87.7 (16.9)	89.2 (15.5)	88.2 (17.3)	90.0 (15.6)	92.9 (9.2)	93.5 (9.0)
	P	0.098	0.011	0.007	0.013	0.002	0.008
	CMT (N=61)	90.7 (16.3)	87.4 (21.4)	81.2 (27.0)	86.7 (21.8)	86.2 (25.7)	94.4 (13.9)

Cognitive functioning	IMT (N=50)	95.3 (11.2)	96.0 (10.9)	96.0 (10.9)	98.2 (7.3)	97.2 (8.3)	98.2 (7.6)
	P	0.091	0.012	<0.001	0.001	0.012	0.171
Social functioning	CMT (N=61)	67.8 (31.8)	62.3 (36.8)	53.6 (37.8)	57.8 (34.9)	62.4 (36.9)	65.4 (31.7)
	IMT (N=50)	77.3 (28.1)	72.7 (34.8)	73.3 (34.3)	79.3 (30.4)	82.1 (25.9)	82.9 (27.9)
	P	0.099	0.133	0.005	0.003	0.008	0.023

SD = Standard Deviation; CMT = Chemotherapy; IMT = Immunotherapy.

Throughout the study, patients reported more symptoms of insomnia (mean score 39.3 ± 33.0), appetite loss (mean score 32.2 ± 32.5), and fatigue (mean score 27.3 ± 26.5) and less burden of nausea/vomiting (mean score 7.6 ± 11.9) and diarrhea (mean score 7.8 ± 18.2). The mean score for all symptom scales was below 50 points for all patients in all treatment cycles. Data regarding symptom scale score differences between treatment groups are presented in Table 4. Symptoms of fatigue and loss of appetite were significantly greater in patients receiving chemotherapy from cycle 2 onwards. Symptoms of nausea/vomiting and constipation, as well as financial difficulties were significantly more in patients receiving chemotherapy in all treatment cycles. However, pain and dyspnea were similar in the two groups in all cycles. Insomnia symptoms were significantly more in patients receiving chemotherapy from cycle 3 onwards, while diarrhea symptoms were significantly more in patients receiving immunotherapy during cycles 5 and 6.

Table 4. Symptom scales score differences between therapy groups.

		Treatment cycles					
Symptom scales (mean, SD) Range 0-100	Treatment groups	1	2	3	4	5	6
Fatigue	CMT (N=61)	25.1 (26.1)	35.2 (29.6)	41.2 (29.1)	37.8 (24.9)	37.1 (25.3)	35.0 (25.7)
	IMT (N=50)	20.9 (28.5)	22.2 (29.9)	23.8 (29.3)	18.8 (25.7)	17.9 (23.8)	13.5 (21.1)
	P	0.108	0.005	0.001	<0.001	<0.001	<0.001
Nausea and vomiting	CMT (N=61)	9.6 (14.4)	11.5 (13.8)	14.5 (16.5)	13.0 (16.2)	12.9 (16.7)	11.7 (15.2)
	IMT (N=50)	2.7 (7.0)	3.0 (8.0)	5.3 (12.3)	3.7 (10.6)	2.4 (7.0)	1.4 (6.1)
	P	0.004	<0.001	<0.001	<0.001	0.001	<0.001
Pain	CMT (N=61)	19.7 (27.5)	24.0 (30.7)	30.3 (31.8)	27.4 (30.4)	26.2 (35.5)	22.2 (31.0)
	IMT (N=50)	22.7 (33.3)	23.7 (33.0)	23.7 (34.0)	18.5 (30.4)	18.3 (27.8)	20.3 (28.6)
	P	0.867	0.810	0.135	0.089	0.387	0.822
Dyspnea	CMT (N=61)	23.5 (31.2)	30.1 (33.7)	37.2 (34.5)	29.6 (30.3)	25.7 (28.1)	21.0 (32.2)
	IMT (N=50)	22.0 (29.8)	21.3 (28.4)	25.3 (31.3)	24.4 (30.5)	17.9 (25.9)	13.5 (22.9)
	P	0.775	0.176	0.065	0.373	0.195	0.432
Insomnia	CMT (N=61)	39.9 (33.2)	45.4 (34.4)	54.1 (30.5)	50.4 (32.3)	45.7 (30.3)	45.7 (28.0)
	IMT (N=50)	29.3 (31.3)	34.0 (37.2)	36.0 (37.4)	34.1 (35.2)	29.3 (33.5)	27.9 (32.9)
	P	0.100	0.092	0.010	0.029	0.027	0.021
Appetite loss	CMT (N=61)	30.1 (32.6)	44.3 (30.9)	45.4 (31.6)	43.7 (30.0)	47.6 (34.6)	50.6 (33.8)
	IMT (N=50)	22.7 (31.9)	26 (37.7)	27.3 (38.5)	18.5 (30.6)	15.5 (28.0)	15.3 (30.0)
	P	0.180	0.002	0.003	<0.001	<0.001	<0.001
Constipation	CMT (N=61)	28.4 (35.9)	32.8 (34.7)	35.5 (35.9)	37.0 (32.7)	35.2 (35.2)	32.1 (36.4)
	IMT (N=50)	5.3 (18.3)	8 (20.8)	9.3 (23.4)	8.9 (26.0)	4.9 (15.9)	3.6 (15.3)
	P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Diarrhea	CMT (N=61)	3.8 (15.0)	5.5 (17.4)	2.7 (9.2)	9.6 (19.6)	5.7 (18.9)	4.9 (15.2)
	IMT (N=50)	4.7 (19.0)	5.3 (17.0)	6.7 (17.8)	10.4 (17.2)	16.3 (26.0)	18.9 (26.7)
	P	0.938	0.986	0.291	0.574	0.021	0.016
Financial difficulties	CMT (N=61)	33.9 (30.7)	36.6 (28.4)	38.8 (32.9)	34.8 (26.6)	32.4 (29.7)	25.9 (25.0)
	IMT (N=50)	19.3 (26.2)	14.0 (19.2)	16.0 (22.6)	12.6 (19.2)	12.2 (19.4)	13.5 (20.0)
	P	0.009	<0.001	<0.001	<0.001	0.001	0.037

SD = Standard Deviation; CMT = Chemotherapy; IMT = Immunotherapy.

4. Discussion

Despite the underreporting of QoL in clinical studies [21,22], its measurement using self-completed instruments can contribute to improving patient care by highlighting needs, such as emotional and spiritual well-being, that would otherwise be overlooked [23]. The main results of our study show that patients with NSCLC reported good total QoL and cognitive, emotional and physical functioning. The scores we recorded are considered higher compared to other studies with cancer patients [24–27]. In a Greek study that examined the quality of life of 95 cancer patients, the general health/QoL was moderate (62.6) and similarly to our study the highest scores were recorded in cognitive (75.4), physical (66.8) and emotional functioning (66.6) [25]. According to another Greek study with a sample of lung cancer patients, the QoL of 168 patients with NSCLC was even lower (57.3), while these patients also reported better emotional (68.6), cognitive (61.8) and physical functioning (57.2), compared to role (49.2) and social functioning (49.9) [26]. These differences can be partially explained by differences in sample size and data collection location, as well as by the patients' different demographic and clinical characteristics.

Regarding QoL, depending on the type of treatment, our findings show that in contrast to the group receiving chemotherapy, patients receiving immunotherapy reported significantly better general health status from the 3rd to the 5th cycle of treatment, with the difference between the two groups being greater in the 5th cycle. Furthermore, from cycle 3 onwards it appears that while the immunotherapy group responded better to the demands of the disease, as well as their participation in social becoming, the chemotherapy group reported reduced role and social functioning. These differences suggest that probably immunotherapy is a better option for patients with advanced NSCLC, as it not only does not worsen, but improves functional scales. In addition, higher emotional and cognitive functioning in the immunotherapy group from cycle 2 onwards highlight the differential effects by treatment group. Our findings agree with previous international studies, which report a better QoL based on the EORTC QLQ-C30 scale, in patients with NSCLC receiving first-line or second-line immunotherapy, compared to patients receiving chemotherapy [28–30]. However, in a study of NSCLC patients who received first-line treatment, there was no difference between patients who received platinum-based chemotherapy versus those who received dorvalumab-based immunotherapy [31].

Regarding symptoms related to the disease and its treatment, in all phases of our study, patients reported a mean score of < 50 on the EORTC QLQ-C30 symptom scales. The highest mean score was observed in insomnia, loss of appetite and fatigue. Conversely, the lowest mean score was observed in nausea/vomiting and diarrhea. Our results are considered similar to other studies in patients with cancer or NSCLC [25,26,32,33]. More specifically, 334 NSCLC patients reported similar mean symptom score (27.2), while the predominant symptoms were dyspnea, fatigue, and insomnia [32]. On the other hand, regarding 230 NSCLC patients, the lowest scores were observed in diarrhea and nausea/vomiting [33].

From the comparative analysis of symptoms by treatment group, it appears that immunotherapy was better tolerated, as symptoms of fatigue and insomnia remained stable, while they increased significantly in patients receiving chemotherapy. In addition, the constipation score was reduced in patients receiving immunotherapy, with no change in the chemotherapy group. Contrary to previous findings, diarrheal symptoms increased significantly in the immunotherapy group, while they did not change in the chemotherapy group. Differences in favor of immunotherapy might have been greater if symptom assessment had not been done before starting treatment, as several docetaxel-related symptoms were expected to worsen after drug administration [34].

A limitation of this study was the small sample size, which is often observed in non-multicenter studies. Additionally, 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 QoL and symptom burden.

5. Conclusions

In conclusion, our study findings demonstrated a good general health status/QoL in NSCLC patients, while despite the varied symptoms related to the disease and its treatment, they reported

moderate burden, with predominant symptoms being insomnia, loss of appetite and fatigue. Comparative analysis of the data showed that QoL improved in the immunotherapy group, who reported less burden from most symptoms compared to the chemotherapy group.

The present study highlights the need for multicenter studies that will evaluate the QoL in larger populations of patients with NSCLC, emphasizing that patient's reports on QoL should be considered necessary to develop new health strategies that could improve the level of health care provided, in terms of treatment, rehabilitation or palliative care of oncology patients.

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Informed Consent Statement: Informed consent was obtained from all patients involved in the study.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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