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ORIGINAL ARTICLE

Association Between Change in Quality of Life and Survival in Advanced Non-Small-Cell Lung Cancer

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OBJECTIVE

In advanced-stage lung cancer, the developments in treatment options have resulted in improved survival and quality of life (QoL) becoming parallelly important. The present study investigates whether the pre-treatment QoL domains and changes in the QoL scores could predict survival rates of patients with non-small-cell lung cancer (NSCLC).

METHODS

We analyzed 50 advanced NSCLC patients. Health-related quality of life (HRQoL) was assessed at baseline, on day 7 and after the second cycle of chemotherapy, using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). The Kaplan-Meier and Cox regression models were used for both univariate and multivariate analyses of survival.

RESULTS

When baseline QoL domains were considered, constipation was predictive of survival on multivariate analysis (hazard ratio [HR], 1.02; 95% confidence intervals [CI], 1.00-1.04; p=0.010). In the multivariate analysis, a relationship was observed between fatigue and survival when considering changes in QoL (HR, 1.03; 95% CI, 1.01-1.04; p≤0.001).

CONCLUSION

Our findings indicate that baseline constipation and changes in fatigue during treatment provide useful prognostic information in advanced NSCLC patients. We can utilize these predictive factors for a patient-based treatment outcome. If necessary, interventions need to be made to improve specific components of QoL before and during the treatment course to benefit the patient's survival.

Keywords: European Organization for Research and Treatment of Cancer; non-small-cell lung cancer; quality of life; survival.

Introduction

Lung cancer is the most common cancer worldwide, in terms of both incidence and mortality, with 2,093,876 new cases and 1,761,007 deaths in 2018.[1] Most patients (approximately 85%) who have lung cancer are diagnosed with non-small-cell lung cancer (NSCLC), and the majority of these patients present with locally advanced or metastatic disease.[2]

In patients diagnosed with lung cancer, several distressing side effects occur before diagnosis and continue the duration of the disease as well as the treatment period, which negatively affect the functional, psychological, and social health and quality of life (QoL) of the

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patient.[3,4] Most patients with advanced NSCLC do not have effective treatment options; therefore, while planning treatment for these patients, the aim should be to prolong survival, as well as to improve the QoL by minimizing the side effects of the treatment.[5]

Health-related quality of life (HRQoL) is a multidomain concept that covers the subjective perceptions of the positive and negative aspects of cancer patients' symptoms, including physical, emotional, social, and cognitive functions and, importantly, the disease symptoms and side effects of treatment.[6] Data derived from HRQoL scoring methods offer comparative treatment options, support for daily clinical considerations of treatment selection, enhance understanding between patient and clinician, and guide attending clinicians to treatment options that are economically viable as well as streamline access to various health-care resources.[7]

Many previous studies have shown the relationship between a patient's baseline HRQoL and overall survival (OS) in several different types of cancers independent of the extent of the disease and other clinical prognostic factors.[8-16] However, few studies have examined the relationship between change in HRQoL and OS.[17-19]

The study presented here analyzes whether or not pre-treatment QoL measurements, as well as changes in QoL scores from baseline, on day 7 and after the second cycle of treatment, could predict survival with patients in Stages III-IV NSCLC.

Materials and Methods

We used data obtained from a clinical trial comparing the association between QoL and disease and treatment factors in advanced NSCLC patients receiving chemotherapy with up-to-date survival data.[20] To be eligible for inclusion in the original trial, patients had to be diagnosed with histologically confirmed NSCLC Stages IIIB and IV. Additional eligibility criteria included patients' written consent to the chemotherapy regimen, presence of an ECOG performance status of 0-2, absence of any concurrent radiotherapy, and the availability of a tumor response assessment after the second cycle of chemotherapy.

We collected additional data for this study from records that included single or combination chemotherapy, type of chemotherapy (platinum or non-platinum), and prior radiotherapy history. Necessary follow-up information, such as date of death or last contact/last known to be alive, was obtained from the local population directorate. This study was approved by the Akdeniz University ethics committee.

QoL Assessment

QoL was assessed before the first cycle, on day 7, and after the completion of the second cycle using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). EORTC QLQ-C30 uses the following: Five functioning scales (physical, role, emotional, cognitive, and social), nine symptom scales (fatigue, pain, dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, nausea, and financial issues), and the global health status/QoL scale. Raw scores were then processed into a linear sense to give standard scores in the range of 0-100 for each scale, both functioning and symptom scales. Elevated scores in the global and functioning scales and decreased scores in the symptom scales indicated better QoL. 5-10 points, the scores indicated a small change, 10-20 points indicated moderate change, and a score above 20 indicated a clinically significant, considerable change on part of the patient's perspective.[21] Turkish validity and reliability analyses of the EORTC QLQ-C30 were performed in the previous studies.[22,23]

Statistical Analysis

Patient survival was the primary endpoint and was defined as the time interval between the date of the patient's first visit to the hospital and the date of death from any cause or the date of last contact/last known to be alive. Three separate analyses were performed. First, the relationship between baseline QoL and patient survival was investigated for 50 patients. Second, the relationship between the change in QoL scores from baseline to day 7 and after the second cycle, as well as survival, was assessed for the same patient cohort. Third, the relationship between baseline QoL and change in QoL scores and patient survival was investigated. The changes in scores were calculated by subtracting the baseline from the QoL scores on day 7 and after the second cycle. The OS was calculated using the Kaplan-Meier method. Clinical and QoL variables were evaluated using univariate Cox proportional hazards models to determine which parameters showed individual prognostic value for survival. Multivariate Cox proportional hazards models were then performed to evaluate the joint prognostic significance of all QoL and clinical factors. Each QLQ-C30 scale was treated as a continuous variable for the purpose of Cox regression analyses. The effect of QoL parameters on patient survival was expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Changes of 10 or more points on a 0-100 scale were considered clinically relevant, so HRs were presented by a 10-point change on the continuous QoL variables.

Turk J Oncol 2022;37(3):246–53
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An effect was considered to be statistically significant if p<0.05 was considered. All statistical tests were two sided. All data were analyzed using Statistical Package for the Social Sciences version 18.0.

Results

The baseline characteristics of our patient cohort are described in Table 1. Among the 37 patients receiving first-line chemotherapy, the proportions having different chemotherapy regimens were as follows: 25 (68%) platinum + etoposide, 4 (11%) platinum+vinorelbine, 4 (11%) platinum+gemcitabine, 1 (3%) platinum+paclitaxel, 2 (5%) vinorelbine alone, and 1 (3%) gemcitabine alone. Of the 13 cases treated with second-line chemotherapy, 6 (46%) had docetaxel only, 3 gemcitabine (23%) only, and 4 (31%) various other regimens. At the time of this analysis, all of our patients were dead. Median OS for the entire patient cohort was 397 days (95% CI: 263-531 days).

Table 2 describes the baseline and change in scores for all aspects of the QLQ-C30 instrument. Baseline scores among the QLQ-C30 functioning scales recorded that role function had the lowest (worst) mean score of 68.6, with the highest (best) mean score being 91.0 for cognitive functioning. Among the QLQ-C30 symptom scales, nausea/vomiting had the lowest (best) mean score of 4.6, while the highest (worst) mean score of 31.3 was noted for fatigue and dyspnea. From baseline to day 7, the biggest improvement was seen in role function, pain, and dyspnea. After the second cycle, the biggest improvement was seen in role function, emotional function, global QoL, and dyspnea.

Results of the univariate Cox regression analysis for baseline patient characteristics and QoL domain are presented in Table 3. The only baseline QoL scale that was predictive of survival was constipation (p=0.04), as per the univariate analysis. Table 3 also presents the results of the univariate Cox regression analysis for change in QoL scores. On day 7, the only QoL variables that were marginally predictive of survival were constipation (p=0.06), while after the second cycle, the following variables were associated with survival: Global health status (p=0.01), physical functioning (p=0.003), social functioning (p=0.03), fatigue (p=0.001), dyspnea (p=0.09), and insomnia (p=0.01). The univariate analysis (p=0.05) also found combination chemotherapy to be a significant predictor of survival. Of note, the median survival for receiving single-agent chemotherapy and combination chemotherapy was 272 and 445 days, respectively, p=0.021. In addition, before the chemotherapy, only 22 patients had constipation while 28 did not. The median survival for patients with and without constipation was 265 and 500 days, respectively, p<0.01. Furthermore, the median figures for OS with respect to change in fatigue compared to baseline and after the second cycle were 288 versus 597 days, p<0.001.

Table 4 describes the results of multivariate Cox regression analyses for baseline patient characteristics and changes in QoL scores. As per the multivariate analysis, the following variables were associated with survival: Baseline constipation (HR, 1.02; 95% CI, 1.00-1.04; p=0.010) and change in fatigue after the second cycle (HR, 1.03; 95% CI, 1.01-1.04; p<0.001). In addition, utilization of platinum-based combination chemotherapy was also found to be statistically significant in the multivariate analysis (HR, 0.40; 95% CI, 0.18-0.87; p=0.021). See Figures 1 and 2 for the association of baseline constipation and change in fatigue after the second cycle with overall survival.

Table 1 Patient characteristics (n=50)

Clinical features	n	%	Mean (SD)	Median	Min	Max
Age			55.9 (10.1)	56.5	36	80
<50	13	26				
50-60	20	40				
>60	17	34				
Gender						
Female	4	8				
Male	46	92				
ECOG performance status						
1	27	54				
2	23	46				
Comorbidity						
Absent	41	82				
Present	9	18				
Previous surgery						
Yes	13	26				
No	37	74				
Chemotherapy						
Single	14	28				
Combination	36	72				
Treatment type						
Platinum based	39	78				
Non-platinum	11	22				
Radiotherapy						
Yes	18	36				
No	32	64				

ECOG: Eastern Cooperative Oncology Group; SD: Standart deviation

Table 2 Quality of life scores

QoL domain	Quality of life score baseline		Quality of life change on day 7		Quality of life change after the second cycle	
	Mean	SD	Mean	SD	Mean	SD
General quality of life						
Global	57.0	24.4	-4.50	23.2	3.07	33.2
General function						
Physical	73.2	25.4	-5.60	22.1	-8.26	28.4
Role	68.6	19.2	5.66	13.7	4.34	19.0
Emotional	81.3	16.7	0.83	11.3	5.97	13.7
Cognitive	91.0	15.8	-0.33	8.5	-2.89	10.7
Social	79.3	19.5	-4.66	10.6	-6.15	12.3
General symptom						
Fatigue	31.3	22.9	7.55	14.6	9.66	26.6
Nausea/vomiting	4.6	10.6	18.66	17.7	7.97	19.1
Pain	28.0	28.2	-3.0	15.6	0.36	24.9
Dyspnea	31.3	32.5	-4.0	17.3	-1.44	28.0
Insomnia	16.6	23.5	0.66	18.4	0.72	22.7
Appetite loss	21.3	28.3	16.0	23.5	11.59	39.2
Constipation	15.3	18.0	2.66	21.1	0.0	23.3
Diarrhea	6.0	17.4	2.66	17.6	-0.72	20.4
Financial	28.0	22.6	2.66	11.3	7.24	17.0

QoL: Quality of life; SD: Standart deviation

Discussion

In this study, we investigated whether baseline QoL as well as changes in QoL on day 7 and after the second cycle of treatment could predict survival in advanced NSCLC. In our study, we found that a statistically significant relationship was found between specific QoL components measured by EORTC-C30 and survival in patients with advanced NSCLC.

Improvements in cancer treatment outcomes have led to an increase in the survival of cancer patients. After the realization that QoL is as important as survival for patients, studies investigating the QoL in various cancer types have increased, especially in the past three decades. However, QoL is rarely evaluated in most clinical oncology practices. The biggest obstacle is the inherent difficulties of its inclusion in intensive clinical practice.[18] Nevertheless, regular QoL assessments and management in daily oncology practices can provide useful information to patients and physicians.

In this study, we found three important results. First, we found better survival in those who received platinum-based combination chemotherapy. Among the 50 patients, 14 of them received single-agent chemotherapy, while 36 received platinum-based combination chemotherapy. The platinum-based combination chemotherapy correlating with better survival has been previously demonstrated in studies in advanced NSCLC.[24-26] For example, Quoix et al. found median OS to be 10.3 months for platinum-based doublet chemotherapy and 6.2 months for monotherapy; 1-year survival was 44.5% and 25.4%, respectively. In another study, Zukin et al. compared single-agent pemetrexed versus the combination of carboplatin and pemetrexed in first-line therapy for patients with advanced NSCLC. The median OS was 5.3 months for pemetrexed and 9.3 months for carboplatin and pemetrexed. All sharing the superiority of the combination chemotherapy approach, in parallel to our findings.

Second, patients' self-reported constipation at baseline provided prognostic information for survival after adjusting for the effects of age, gender, ECOG performance status, comorbidity, treatment types, radiotherapy, surgery, and other QoL variables. Patients who had less constipation at pre-treatment had favorable survival. The relationship between constipation and survival in lung cancer has been shown in a previous study.[27] Brown et al. reported global QoL, role functioning, fatigue, appetite loss, and constipation to be significant prognostic factors for survival in the multivariate model

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Table 3 Univariate analysis of survival of baseline and change in HRQoL scores

	Baseline		Change from baseline on day 7		Change from baseline after the second cycle	
Patient characteristics and QoL variables	**Univariate HRs (95% CI)**	**p**	**Univariate HRs (95% CI)**	**p**	**Univariate HRs (95% CI)**	**p**
Age	0.99 (0.98-1.00)	0.96				
Gender	0.76 (0.27-2.15)	0.61				
ECOG	1.24 (0.82-1.89)	0.29				
Comorbidity	0.62 (0.29-1.29)	0.20				
Single or combination chemotherapy	1.85 (0.98-3.51)	**0.05**				
Platinum-based or other chemotherapy	1.38 (0.70-2.74)	0.34				
Radiotherapy	0.63 (0.35-1.15)	0.14				
Surgery	0.30 (0.04-2.35)	0.25				
General quality of life						
Global	1.00 (0.99-1.02)	0.19	0.99 (0.98-1.00)	0.19	0.98 (0.97-0.99)	**0.01**
General function						
Physical	1.00 (0.99-1.01)	0.82	1.00 (0.99-1.01)	0.69	0.98 (0.97-0.99)	**0.003**
Role	1.00 (0.98-1.01)	0.78	1.00 (0.98-1.02)	0.80	0.99 (0.98-1.01)	0.85
Emotional	0.99 (0.98-1.01)	0.87	1.00 (0.98-1.03)	0.56	0.99 (0.97-1.02)	0.82
Cognitive	1.00 (0.98-1.01)	0.88	0.99 (0.96-1.02)	0.60	0.98 (0.95-1.01)	0.28
Social	1.00 (0.98-1.01)	0.85	0.99 (0.96-1.02)	0.79	0.97 (0.94-0.99)	**0.03**
General symptom						
Fatigue	1.00 (0.98-1.01)	0.95	1.00 (0.98-1.02)	0.79	1.02 (1.00-1.03)	**0.001**
Nausea/vomiting	1.00 (0.97-1.02)	0.94	0.99 (0.97-1.00)	0.22	0.99 (0.97-1.01)	0.46
Pain	0.99 (0.98-1.00)	0.80	1.01 (0.99-1.02)	0.20	1.00 (0.99-1.02)	0.24
Dyspnea	0.99 (0.98-1.00)	0.43	1.00 (0.98-1.02)	0.44	1.00 (0.99-1.02)	**0.09**
Insomnia	0.99 (0.98-1.00)	0.20	1.00 (0.99-1.02)	0.48	1.02 (1.00-1.04)	**0.01**
Appetite loss	0.99 (0.98-1.00)	0.12	1.00 (0.99-1.01)	0.16	1.00 (0.99-1.01)	0.14
Constipation	1.01 (1.00-1.03)	**0.04**	0.98 (0.96-1.00)	**0.06**	0.99 (0.97-1.00)	0.14
Diarrhea	0.99 (0.97-1.00)	0.27	1.00 (0.98-1.01)	0.79	0.99 (0.98-1.01)	0.90
Financial	0.99 (0.98-1.00)	0.54	1.00 (0.97-1.02)	0.98	0.99 (0.97-1.01)	0.54

HRQoL: Health-related quality of life; QoL: Quality of life; HRs: Hazard ratios; CI: Confidence intervals; ECOG: Eastern Cooperative Oncology Group

at 12 weeks. Similar to our study, survival was longer for those patients with less pre-treatment constipation.

Third, a deterioration in fatigue during treatment is associated with poorer patient survival after adjusting for other covariates. The relationship between pre-treatment fatigue and survival in the lung cancer has been shown in the previous studies.[10,27-29] For example, Herndon et al.[28] reported that the following parameters predicted significantly poorer survival in univariate analyses; increased loss of appetite, pain, fatigue, symptoms of lung carcinoma, poorer overall QoL, and poorer physical function. However, the only EORTC subscale of prognostic importance was the pain subscale in the final multivariate model. In another study, Braun et al.[10] found all five functioning scales, fatigue, nausea/vomiting, dyspnea, loss of appetite, constipation, and diarrhea to be significant predictors of survival. How-

Table 4 Multivariate analysis of survival of baseline and change in HRQoL scores

	Multivariate HRs (95% CI)	**p**
Singe or combination chemotherapy	0.40 (0.18-0.87)	**0.02**
Constipation[a]	1.02 (1.00-1.04)	**0.01**
Constipation[b]	0.99 (0.97-1.01)	0.52
Global[c]	0.99 (0.97-1.00)	0.11
Physical[c]	0.99 (0.97-1.00)	0.32
Social[c]	0.99 (0.96-1.01)	0.49
Fatigue[c]	1.03 (1.01-1.04)	**<0.001**
Dyspnea[c]	1.00 (0.99-1.01)	0.33
Insomnia[c]	1.01 (0.99-1.03)	0.17

[a]: Baseline quality of life variable; [b]: On day 7 quality of life variable; [c]: After the second cycle quality of life variable. HRQoL: Health-related quality of life; HRs: hazard ratios; CI: Confidence intervals

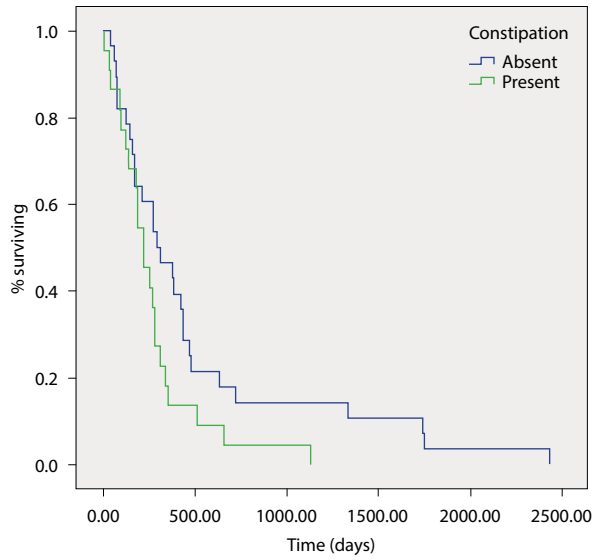

Fig. 1. Baseline constipation and overall survival.

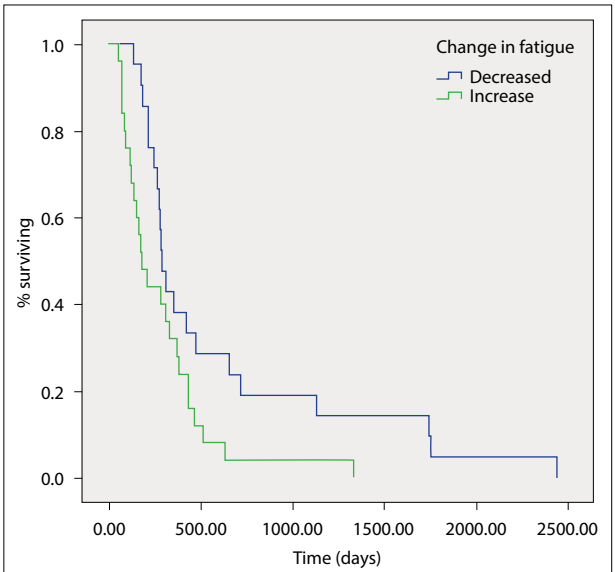

Fig. 2. Change in fatigue from baseline after the second cycle and overall survival.

ever, global QoL and physical functioning predicted patient survival in the final multivariate model. Furthermore, change in fatigue predicting survival in another type of cancer has also been reported.[30] Djärv et al. reported that survival was longer in patients with esophagogastric cancer who had fewer problems with dyspnea before treatment and better recovery in physical function, pain, and fatigue after treatment.

In our study, we only evaluated NSCLC Stage IIIB and IV patients. Furthermore, there are studies examining the prognostic role of QoL in patients with NSCLC at different stages. For example, Braun et al.[10] reported that the study population consisted of 1194 NSCLC of different stages. On multivariate analyses, in the advanced study population, global QoL as well as physical function predicted patient survival. This highlights the importance of QoL in the advanced population and is parallel to our findings. In the literature, some studies do report on survival in Stage IIIB wet, with pleural effusion, and Stage 4 patients, combined.[31,32] Our study similarly reports on this combined stage.

Our findings have certain implications that can be used in clinical and research practices. When planning treatment, in addition to clinical variables, baseline HRQoL should also be taken into account and regular QoL measurements should be made during the treatment course. In a nutshell, we think that in addition to clinical prognosticators, baseline and repeating measurements of QoL parameters may add to improved prognostication of advanced NSCLC.

Conclusion

This study suggests that platinum-based combination chemotherapy, baseline constipation, and changes in fatigue after the second cycle during the treatment course provide useful prognostic information in advanced NSCLC patients.

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Ethics Committee Approval: The study was approved by the Akdeniz University Non-interventional Clinical Research Ethics Committee (No: 85, Date: 06/03/2012).

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Turk J Oncol 2022;37(3):246–53
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