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The Effect of Metformin on Survival in Patients with Non-Small Cell Lung Cancer

Ali Caner ÖZDÖVER[1], Evren FİDAN[1]*, Şafak YILDIRIM DİŞLİ[1], Nejla RAKICI[2], Nazlı KAZAZ[1]

ABSTRACT

Aim: Lung cancer is the most common cause of cancer- related deaths in the world. Diabetes mellitus (DM) can be seen frequently in the lung cancer patient group as well as in the normal population. Metformin is one of the most commonly used biguanide drugs in the treatment of DM. Studies conducted in patients with different types of cancer, such as breast, liver, and prostate, have shown that metformin use may contribute to survival. The aim of the study is to evaluate the effect of metformin on survival in patients with non-small cell lung cancer (NSCLC).

Matherial and Methods: In this study, 85 patients diagnosed with non-small cell lung cancer and concurrent type 2 DM retrospectively were analyzed, and the last follow-up date was 31.11.2020. Neutrophil/lymphocyte ratio (NLR) of the patients was calculated. Alkaline phosphatase (ALP), lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA) values and their contribution to survival were examined.

Results: The 1, 3, and 5-year overall survival rates for all patients were 76.0%, 46.5%, and 34.3%, respectively, and the median OS was 64.1 (95% CI: 44.7-83.5). Lymph node (LN) positivity, liver metastasis, and death rates were less common in the patient group receiving metformin. Overall survival (OS) results and determined survival rates were worse in the non-metformin patient group.

Conclusion: Metformin usage and the control of hyperinsulinemia and hyperglycemia may contribute to survival rates. Larger and prospective studies are needed to determine the effect of metformin which is used for glycemic control and insülin resistance, in NSCLC patients' survival.

Keywords: Metformin; diabetes; lung cancer.

Küçük Hücreli Dışı Akciğer Kanserli Hastalarda Metforminin Sağkalıma Etkisi

ÖZ

Amaç: Akciğer kanseri dünyada kansere bağlı ölümlerin en sık nedenidir ve bu hastalarda normal popülasyonda olduğu gibi Diabetes Mellitus (DM) görülebilir. Metformin diyabet tedavisinde en sık kullanılan biguainiddir. Meme, karaciğer ve prostat gibi farklı kanser türlerine sahip hastalarda yapılan çalışmalar, metformin kullanımının hayatta kalmaya katkıda bulunabileceğini göstermiştir. Bu çalışmanın amacı, küçük hücre dışı akciğer kanserli (KHDAK) hastalarda metforminin sağkalım üzerine etkisini değerlendirmektir.

Gereç ve Yöntemler: Çalışmamıza 85 eş zamanlı diyabet tanısı olan hasta dahil edilmiştir. DM tanısı için metformin kullanmayan hastalar kontrol grubu olarak alındı. Sağkalım analizi için son takip tarihi 31 Kasım 2020 olarak belirlendi. Hastaların nötrofil/lenfosit oranı (NLO) hesaplandı, alkalen fosfataz (ALP), laktat dehidrojenaz (LDH), karsinoembriyonik antijen (CEA) değerleri ve sağ kalıma katkıları incelendi.

Bulgular: Tüm hastalarda 1,3 ve 5 yıllık genel sağkalım oranları sırasıyla %76,0, %46,5 ve %34,3 ve medyan OS 64,1 (%95 GA: 44,7-83,5) olarak belirlendi. Lenf nodu pozitifliği, karaciğer metastazı ve ölüm oranları metformin alanlarda daha az sıklıkta görülmüştür. Genel sağkalım sonuçları ve sağkalım oranları metformin kullanmayan hastalarda daha kötüdür.

Sonuç: Metformin kullanımı ile beraber hiperinsülinemi ve hipergliseminin kontrol altına alınması sağkalıma katkı sağlayabilir. Glisemik kontrol ve insülin direnci amacıyla kullanılan metforminin KHDAK hastalarının sağ kalımına etkisinin belirlenmesi için daha geniş ve prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Metformin; diyabet; akciğer kanseri.

1 Karadeniz Technical University, Faculty of Medicine, Department of Medical Oncology, Trabzon, Turkey
2 Karadeniz Technical University, Faculty of Medicine, Department of Internal Medicine, Trabzon, Turkey

Sorumlu Yazar / Corresponding Author: Evren FİDAN, e-mail: evrenkarafidan@yahoo.com
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INTRODUCTION

The incidence and mortality rates of lung cancer are still high and it is the second cause of death in cancer statistics (1). Non-small cell lung cancer (NSCLC) accounts for 80-85% of all lung cancer cases and when the diagnosis is made in the early stage, curative surgical treatment can be applied (2). However, the rate of patients who can undergo curative surgical resection does not exceed 25-30% of all lung cancer cases. 5-year survival rates of resectable cases reach 75% for stage 1 patients; it can reach 15% for stage 3 patients (3,4). Diabetes mellitus (DM) is a common comorbid disease in the lung cancer patient population as well as in the general population. Although it cannot be shown certainly that the incidence of cancer development in patients with DM diagnosis is increased, it has been found that DM diagnosis is a common comorbidity in cancer patients (2,5). Metformin is the most commonly used biguanide drug in the treatment of type-2 DM. Studies conducted in patients with different types of cancer, such as breast, liver, and prostate, have shown that metformin use may contribute to survival (6,7). Considering the negative effects of hyperglycemia and hyperinsulinemia in carcinogenesis, it is thought that the decrease in insulin secretion together with the use of metformin provides anti-tumoral efficacy (8). Reducing the amount of adenosine 5'-monophosphate-activated protein kinase (AMK), inducing apoptosis, and decreasing tumor proliferating kinases are the other important anti-tumoral mechanisms of metformin (8,9). The mammalian target of the rapamycin (mTOR) pathway, which has an important role in cell proliferation, is inhibited by metformin (10). It is also thought metformin inhibits hexokinase in glycolytic enzyme pathways in vitro and induces apoptosis by reducing glucose reuptake in this way (6).

This study was designed to evaluate the contribution of metformin use to survival in the diagnosis of concomitant DM in non-small cell lung cancer cases retrospectively.

MATERIAL AND METHODS

The study included 85 patients diagnosed with non-small cell lung cancer and concurrent type 2 DM, who applied to Karadeniz Technical University, Department of Medical Oncology between 1.1.2010-31.12.2015. Patients who did not use metformin for the diagnosis of DM were taken as the control group. The effects of metformin use on disease-free survival (DFS) in patients with operated lung cancer and on overall survival in all patients were investigated. Patients who developed DM complications and those with type 1 diabetes were excluded from the study. The last follow-up time was determined as 31 November 2020 for survival analysis. The neutrophil/lymphocyte ratio (NLR) of the patients was calculated, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA) values, and their contribution to survival were examined. Computed tomography (CT) reports routinely performed on patients for metastasis screening were reviewed, and brain magnetic resonance imaging (MRI) reports for brain metastases were reviewed. The patients' surgical pathology, clinical and demographic data, and dates required for survival analysis were retrospectively scanned from the electronic system of the hospital. The research was conducted out in line with the principles of the Declaration of Helsinki and was approved by the local ethical committee (No. 2019/46). Due to the retrospective nature of the study, informed consent was not required from the patients.

Statistically Analysis

Data analysis was performed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). Kolmogorov-Smirnov test was used to investigate whether the normal distribution assumption was met. Categorical data were expressed as numbers (n) and percentages (%) while quantitative data were given as mean±SD and median (IQR: 25th – 75th) percentiles. While the mean differences between groups were compared by Student's t test, otherwise the Mann Whitney U test was applied for the comparisons of not normal distributed variables. Categorical data were analyzed $\chi 2$ or Fisher's exact test, where appropriate. Whether the difference in NLR levels between pre- and post-op within groups were statistically significant or not was evaluated Wilcoxon Sign Rank test. Kaplan-Meier survival analysis via log-rank test was used for determining whether metformin usage had a statistically significant effect on prognosis (i.e., DFS and OS). Cumulative survival rates for 1, 3, and 5 years, mean expected duration of life and 95% confidence intervals were computed. Whether the potential factors had a statistically significant effect on prognosis or not was investigated univariate Cox's proportional hazard regression models. Multiple Cox's proportional hazard regression model was obtained to determine the best independent predictors which mostly affected on prognosis. Any variable whose univariable test had a p value <0.10 was accepted as a candidate for the multivariable model. Hazard ratios (HR), 95% confidence intervals, and Wald statistics for each independent variable were also calculated. A p value less than 0.05 was considered statistically significant.

RESULTS

In this study, 85 NSCLC patients were included. Descriptive demographic and clinical characteristics are shown in Table 1. There was no statistical difference in terms of age, gender, smoking, pathology findings, lymph node status, ALP, NLR, CEA and the history of adjuvant chemotherapy (p>0.05). LN positivity, liver metastasis and mortality rates were significantly higher in non-metformin group (p=0.006, p=0.010 and p=0.024).

The results of DFS and OS according to the metformin use are shown in Table 2. Among the operated patients (n= 32), the rates of 1,3 and 5 year DFS rates were 86.2%, 78.9% and 64.1% respectively and median DFS was 96.4 months (95% CI: 71.9-120.9). There was no statistical difference in all operated patients group according to DFS (p=0.771). Figure 1 shows the Kaplan- Meier curves in

Table 1. Baseline demographic and clinical characteristics of participants

	Total (n=85)	No Metformin (n=28)	Metformin (n=57)	p-value
Age (year) (mean±SD)	63.3±9.3	63.7±7.7	63.1±10.0	0.765†
Sex (n/%)				0.093‡
Male	73 (85.9)	27 (96.4)	46 (80.7)	
Female	12 (14.1)	1 (3.6)	11 (19.3)	
Smoking status (n/%)	71 (83.5)	25 (89.3)	46 (80.7)	0.371‡
Pathology (n/%)				0.803¶
Adenocarcinoma	54 (63.5)	19 (67.8)	35 (61.4)	
SCC	26 (30.6)	8 (28.6)	18 (31.6)	
Others	5 (5.9)	1 (3.6)	4 (7.0)	
Lymph node (n/%)	57 (67.9)	25 (89.3)	32 (57.1)	**0.006¥**
Sites of metastasis (n/%)	55 (64.7)	22 (78.6)	33 (57.9)	0.102¥
Brain	13 (15.3)	2 (7.1)	11 (19.3)	0.205‡
Bone	24 (28.2)	8 (28.6)	16 (28.1)	>0.999¥
Lung	11 (12.9)	5 (17.9)	6 (10.5)	0.493‡
Liver	4 (4.7)	4 (14.3)	0 (0.0)	**0.010‡**
Adrenal	4 (4.7)	3 (10.7)	1 (1.8)	0.102‡
Others	2 (2.4)	0 (0.0)	2 (3.5)	>0.999‡
Number of positive lymph nodes (n/%)				0.055¶
0	16 (59.3)	4 (57.1)	12 (60.0)	
1	6 (22.2)	0 (0.0)	6 (30.0)	
2	3 (11.1)	1 (14.3)	2 (10.0)	
3	2 (7.4)	2 (28.6)	0 (0.0)	
ALP	96.0 (81.5-127.5)	96.5 (83.7-129.5)	94.0 (79.5-127.0)	0.452§
LDH	204.0 (170.5-264.0)	204.5 (176.2-303.7)	204.0 (168.0-241.0)	0.691§
NLR	3.30 (1.91-5.62)	3.37 (2.02-8.70)	3.15 (1.91-5.19)	0.424§
CEA	3.0 (2.4-6.0)	3.0 (2.2-6.7)	3.0 (2.4-6.0)	0.866§
Adjuvant chemotherapy (n/%)	32 (37.6)	6 (21.4)	26 (45.6)	0.054¥
Status (n/%)				**0.024¥**
Alive	31 (36.5)	5 (17.9)	26 (45.6)	
Exitus	54 (63.5)	23 (82.1)	31 (54.4)	

† Student's t test, ‡ Fisher's exact test, ¶ Fisher Freeman Halton test, ¥ Continuity corrected χ^2 test, § Mann Whitney U testi. Abbrevations: SCC= squamous cell carcinoma, ALP= alcalyne phosphatase, LDH= lactate dehydrogenase, NLR= neutrophile lymphocyte ratio, CEA= carcinoembryonic antigen

Table 2. Kaplan Meier Survival Analyse: DFS and OS rates of patients

DFS	**N**	**Cumulative survival rates**			**Expected median survival†**	**Log-Rank**	**p-value**
		1-year	*3-year*	*5-year*	*Months*		
Metformin						0.085	0.771
No	7	71.4	71.4	57.1	69.0 (35.4-102.5)		
Yes	25	90.9	81.1	66.3	96.4 (67.7-125.1)		
Metastatic						1.996	0.158
No metformin	3	33.3	33.3	N/A	18.9 (0.0-46.8)		
Metformin	8	75.0	50.0	25.0	51.5 (14.4-88.4)		
General	32	86.2	78.9	64.1	96.4 (71.9-120.9)	-	-

Overall survival	**N**	**Cumulative survival rates**			**Expected median survival†**	**Log-Rank**	**p-value**
		1-year	*3-year*	*5-year*	*Months*		
Metformin						4.206	**0.040**
No	28	71.4	28.6	17.9	33.2 (20.7-45.7)		
Yes	57	78.3	57.4	43.6	76.9 (51.1-102.7)		
Metastatic						2.593	0.107
No metformin	22	68.2	18.2	N/A	22.2 (15.4-29.0)		
Metformin	33	72.7	43.5	31.6	49.9 (29.8-69.9)		
Operated						1.153	0.283
No metformin	7	100.0	57.1	42.9	56.0 (28.6-83.3)		
Metformin	25	87.4	77.4	70.9	94.1 (65.5-122.7)		
General	85	76.0	46.5	34.3	64.1 (44.7-83.5)	-	-

† Data for expected duration of life was expressed as mean (95% confidence interval), N/A: Not applicable.

operated group according to metformin intake.

In all patients the rates of 1,3 and 5 year overall survival rates were 76.0%, 46.5% and 34.3% respectively and median OS was 64.1 (95% CI: 44.7-83.5). The Kaplan-Meier curves of OS are shown in Figure 2. The OS outcomes and expected lifetime were worse in non-metformin group (p=0.040). There was no statistically significant difference in operated patients according to OS (p=0.283). There was no statistically significant difference between the metastatic group according to metformin intake (p=0.107).

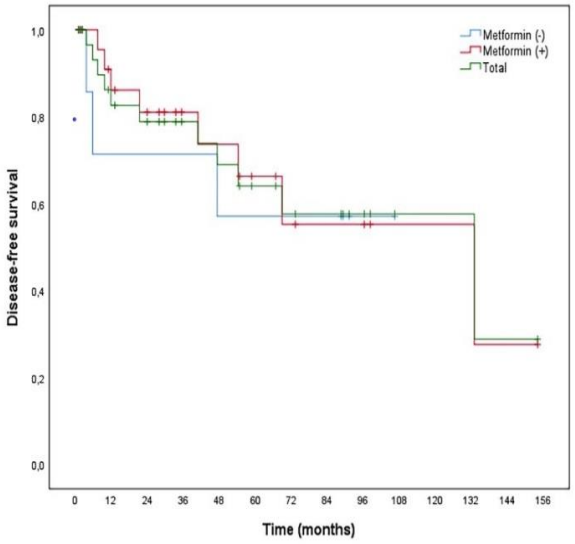

Figure 1. Disease-free survival of the patients

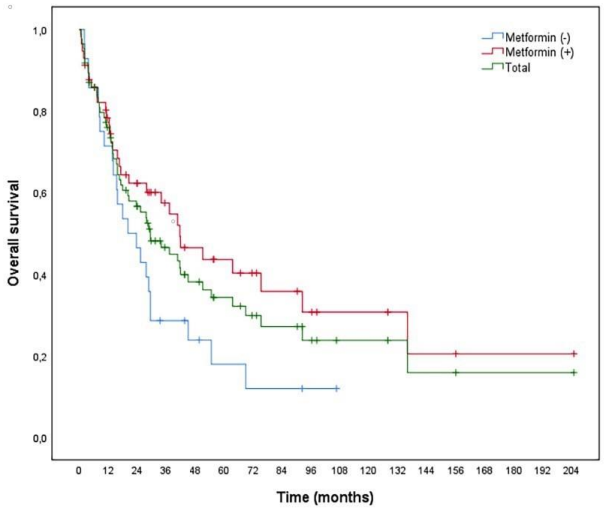

Figure 2. Overall survival of the patien

As a result of univariate analysis, the presence of metastases, ALP levels, and increase in NLR levels had significant effects on DFS. As a result of univariate analysis, all variables determined as p<0.10 were included in Cox regression analysis. The most determining factors in DFS were metastatic stage, ALP and NLR (Table 3). As a result of univariate analysis, NLR, CEA, the presence of metastasis, metformin intake and not receiving adjuvant chemotherapy had significant effects on overall survival. As a result of univariate analysis, all variables determined as p<0.10 were included in cox regression analysis. The most determining factors were increase in CEA levels, increase in NLR levels, the presence of metastases, not receiving adjuvant chemotherapy and increase in ALP levels (Table 4).

Table 3. Results of univariate and multivariate Cox proportional regression analyse: Prognostic factors for DFS

	Univariate analyses					**Multivariate analysis**				
	HR	*LL*	*UL*	*Wald*	*p*	*HR*	*LL*	*UL*	*Wald*	*p*
Age at diagnosis	1.026	0.958	1.099	0.546	0.460	-	-	-	-	-
Male sex	32.581	0.016	N/A	0.801	0.371	-	-	-	-	-
Lymph node positivity	2.757	0.593	12.814	1.673	0.196	-	-	-	-	-
Presence of metastasis	23.741	3.009	187.339	9.031	**0.003**	18.283	2.173	153.846	7.150	**0.007**
No adjuvant therapy	0.453	0.097	2.125	1.009	0.315	-	-	-	-	-
ALP	1.019	1.005	1.033	6.794	**0.009**	1.028	1.007	1.050	7.128	**0.008**
LDH	0.995	0.987	1.004	1.031	0.310	-	-	-	-	-
NLR	1.095	1.027	1.169	7.627	**0.006**	1.172	1.041	1.319	6.879	**0.009**
CEA	0.999	0.995	1.004	0.127	0.722	-	-	-	-	-
No metformin	1.226	0.312	4.822	0.085	0.771	-	-	-	-	-
Smoking status	22.288	0.001	N/A	0.174	0.676	-	-	-	-	-
Delta NLR	0.934	0.855	1.020	2.330	0.127	-	-	-	-	-

HR: Hazard ratio, LL: Lower limits of 95% CI for HR, UL: Upper limits of 95% CI for HR, N/A: Not applicable Abbrevations:, ALP= alcalyne phosphatase, LDH= lactate dehydrogenase, NLR= neutrophile lymphocyte ratio, CEA= carcinoembryonic antigen

Table 4. Results of univariate and multivariate Cox proportional regression analyse: Prognostic factors for OS

	Univariate analyses					**Multivariate analysis**				
	HR	*LL*	*UL*	*Wald*	*p*	*HR*	*LL*	*UL*	*Wald*	*p*
Age at diagnosis	1.048	1.012	1.086	6.925	**0.009**	1.019	0.980	1.060	0.936	0.333
Male sex	1.654	0.707	3.874	1.345	0.246	-	-	-	-	-
Adenocarcinoma	1.270	0.390	4.137	0.158	0.691	-	-	-	-	-
SCC	1.455	0.419	5.046	0.349	0.555	-	-	-	-	-
Lymph node positivity	1.933	0.988	3.784	3.703	0.054	1.173	0.528	2.604	0.154	0.695
Presence of metastasis	3.200	1.624	6.308	11.290	**<0.001**	2.462	1.116	5.432	4.977	**0.026**
No adjuvant therapy	1.813	1.013	3.244	4.018	**0.045**	2.224	1.088	4.547	4.796	**0.029**
ALP	1.005	1.000	1.011	3.714	0.054	1.007	1.001	1.013	4.383	**0.036**
LDH	1.000	0.999	1.001	0.354	0.552	-	-	-	-	-
NLR	1.081	1.042	1.121	17.511	**<0.001**	1.060	1.011	1.112	5.779	**0.016**
CEA	1.011	1.005	1.017	13.572	**<0.001**	1.009	1.003	1.015	10.205	**<0.001**
Smoking status	1.472	0.629	3.446	0.793	0.373	-	-	-	-	-
No metformin	1.760	1.018	3.043	4.092	**0.043**	1.249	0.677	2.305	0.508	0.476

HR: Hazard ratio, LL: Lower limits of 95% CI for HR, UL: Upper limits of 95% CI for HR Abbrevations: SCC= squamous cell carcinoma, ALP= alcalyne phosphatase, LDH= lactate dehydrogenase, NLR= neutrophile lymphocyte ratio, CEA= carcinoembryonic antigen

DISCUSSION

In this study, the survivals of patients with NSCLC and type 2 DM using metformin were examined. The co-existing of type 2 DM and lung cancer has been examined in some studies and the effect of metformin was also examined (11,12). Hyperinsulinemia and insulin resistance may contribute to carcinogenesis and in addition, agents used in type 2 DM for glycemic control may cause anti-cancer effects in NCSLC (13). The role of insulin receptors and insulin-like growth factor receptors in carcinogenesis may explain this effect. These receptors cause cellular transformation, growing, and anti-apoptotic effects. It has been determined that these two receptors are highly expressed in lung cancer patients and cause treatment resistance. For this reason, it is thought that metformin may have positive effects on both reducing treatment resistance and preventing disease progression (14,15). In our study overall survival of all patients and the DFS of operated patients were examined. Although DFS was not statistically significant in operated patients using metformin, their survival was longer and it was approximately 30 months. When the overall survival in all patients was examined, survival was longer in the metformin group and after a 5-year follow-up, %43.6 of the patients were still alive. It was determined that the overall survival results of the operated patients receiving metformin were longer numerically. These findings were found to be consistent with some studies in the literature. In a study performed by Brancher et al., the relationship between metformin use before and after the diagnosis and survival was examined and it was found that metformin prolongs survival (5). In our study, it was determined that 31 patients were still alive until the last follow-up date 31 November 2020 and 26 of the surviving patients were in the metformin group.

Another anti-cancer mechanism of metformin is decreasing the AMP and AMK levels. By acting the AMPK pathway, it causes the inhibition of protein synthesis, suppresses the cancer stem cells, decreases the inflammation (14,16). In this study, we examined the effect of metformin on an inflammatory parameter, NLR. When the operated patient group was examined, no relationship was found between the metformin use and NLR levels. However, when analyses are made on the factors that may affect OS and DFS, it is found that an increase in NLR alone may worsen both DFS and OS. The effect of metformin on NLR levels was not clearly identified at the end of the study and we think this result is related to the small number of patients.

When the patients data were evaluated, it was found that not receiving adjuvant chemotherapy has a negative effect on survival. The patients in the adjuvant group received platin-based chemotherapy. In preclinical studies, metformin has been found to increase the anti-cancer effect of platinum derivates and the AMPK-mTOR, ERK ½, NK-kB pathways were thought to be related to this effect (17,18). In one study, 75 patients who received platinum-based chemotherapy and additional metformin were evaluated and no effect on survival was found (19). In our study, the survival results of those who used metformin and received chemotherapy were numerically longer. However, this difference was not statistically significant.

The most important limitations of the study were the number of patients and its retrospective nature. It has been difficult to identify the patients diagnosed with NSCLC and type 2 DM and using metformin retrospectively. Although it was designed with a limited number of patients, the use of metformin was found to prolong the survival of these patients.

CONCLUSION

Metformin usage and the control of hyperinsulinemia and hyperglycemia contributed to survival rates. Larger and prospective studies are needed to determine the effect of metformin which is used for glycemic control and insülin resistance, in NSCLC patients' survival.

Authors's Contributions: Idea/Concept: A.C.Ö., E.F., Design: E.F., N.K.; Data Collection and/or Processing: A.C.Ö., Ş.Y.D. N.R; Analysis and/or Interpretation: E.F., Ş.Y.D; Literature Review: A.C.Ö., N.R., N.K.; Writing the Article: A.C.Ö., E.F; Critical Review: E.F., N.K.

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