Does the Waiting Period for Genetic Tests Affect the Prognosis in Chemotherapy-Treated de novo Metastatic Non-Small Cell Lung Cancer Patients without a Driver Mutation?

Serdar Arici^a Abdullah Sakin^b Ruhper Cekin^a Saban Secmeler^a
Nurgül Yasar^a Sener Cihan^a

^aDepartment of Medical Oncology, University of Health Sciences, Okmeydani Training and Research Hospital, Istanbul, Turkey; ^bDepartment of Medical Oncology, Yuzuncu Yil University Medical School, Van, Turkey

Keywords

Duration between diagnosis and the start of first-line chemotherapy · Non-small cell lung cancer · Driver mutations

Abstract

Introduction: The length of the necessary waiting period to test driver mutations may generate anxiety in patients and clinicians. For this reason, an investigation was conducted to determine whether the duration between diagnosis and the start of first-line chemotherapy (DDC) in non-small cell lung cancer (NSCLC) patients without driver mutations has an impact on prognosis. **Methods:** The study included 303 de novo metastatic NSCLC patients without a driver mutation and patients were divided into 2 groups according to DDC: ≤30 days (group A) or >30 days (group B). The determinant factors for progression-free survival (PFS) and overall survival (OS) were examined by Cox regression analysis. **Results:** The mean DDC was calculated as 38.2 ± 54.5 days. The number of patients in group A and B were 183 and 120, respectively. The median PFS in groups A and B was 5.0 and 6.0 months ($p = 0.268$) and the median OS was 10.0 and 11 months, respectively ($p = 0.341$). Univariate and multivariate analyses revealed that DDC was not a factor associated with PFS and OS. **Conclusion:** Our results show that a higher DDC was not associated with a worse prognosis in metastatic NSCLC patients without driver mutations. In this context, it is safer for patients and their physicians to wait for test results before starting chemotherapy.

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Introduction

Lung cancer (LC) is the most common cancer worldwide and the most common cause of cancer-related death. In 2012, approximately 1.8 million patients had LC worldwide, with 1.6 million deaths occurring in the same year. Due to recent innovations and developments in LC treatment, mortality has started to decrease in both men and women, but prognosis is still poor, with the 5-year survival rate being <15%. Non-small cell LC (NSCLC) accounts for 85% of all LC cases [1, 2]. Adenocarcinoma (AC) and squamous cell carcinoma (SCC) are the most common types of NSCLC [3, 4].

The presence or absence of a driver mutation, such as mutated epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) rearrangements, c-ROS oncogene 1 (ROS 1), and increasingly other mutations for which a specific inhibitor is available, is a key determining factor in the choice of initial therapy for patients with advanced lung AC or selected SCC, for example those with a history of light smoking or no smoking at all, and other non-small cell carcinomas not otherwise specified (NSCLC-NOS) [5, 6]. Mutations in the EGFR, ALK rearrangements, and ROS 1 are observed in approximately 20–25% of NSCLC and patients with a driver mutation usually treated with specific inhibitors (e.g., erlotinib, gefitinib, osimertinib, and alectinib) that show significant improvement compared to standard chemotherapy (CT) regimens [7–13]. Initial systemic therapy options for those without a driver mutation (approx. 75% of patients)

are immunotherapy, immunotherapy plus CT, or CT alone when immunotherapy is contraindicated or unavailable [2, 14–16]. Delayed treatment initiation has been evaluated for a variety of solid tumors (early-stage NSCLC, breast, prostate, kidney, pancreas) treated with curative intent and was shown to be increasingly common and to negatively affect survival [17].

However, due to testing after accumulation, a need to re-biopsy, and most frequently delays in accessing preparations, tests for driver mutations take between 4 and 6 weeks. The length of this waiting period may generate anxiety in patients and clinicians alike over a possible delay in selecting a treatment and subsequent decrease in the chance of survival [18]. For this reason, an investigation was conducted into whether the duration between diagnosis and the start of first-line CT (DDC) in NSCLC patients without driver mutations has an impact on prognosis.

Materials and Methods

Study Population

The medical records of 817 patients with de novo metastatic NSCLC who had been treated with palliative CT between 2014 and 2019 in the medical oncology clinic of Istanbul were scanned. The patient staging procedure was performed according to the imaging outcomes of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography, computed tomography, and brain magnetic resonance. The following parameters were defined as exclusion criteria: aged <18 years, patients with a second primary malignancy, those with benign or malign hematological disorder, patients without evidence of metastasis at diagnosis, prior exposure to tyrosine kinase inhibitors or immunotherapy, those with missing data, patients with driver mutation, and patients whose mutation status could not be evaluated. Also, patients were divided into 2 groups according to DDC: ≤30 days (group A) or >30 day (group B; Fig. 1).

Data Collection

Demographic and disease characteristics such as age, gender, smoking history, Eastern Cooperative Oncology Group (ECOG) status, comorbidities (e.g., hypertension [HT], chronic obstructive pulmonary disease [COPD], diabetes mellitus [DM], and coronary artery disease [CAD]), date of diagnosis, histology (NSCLC-NOS, SCC, and AC), grade, stage, metastasis status (oligo [the number of metastasis ≤3] or multiple [the number of metastasis >3]), site of metastasis (brain, contralateral lung, liver, surrenal glands, bone, pleura, and others), grade, mutational status (EGFR, ALK, and ROS 1), start date of first-line CT, CT regimens (platinum + pemetrexed, platinum + paclitaxel, platinum + docetaxel, platinum + gemcitabine, platinum + etoposide, and platinum + vinorelbine), number of CT cycles, progression date, and last status (deceased or alive), were obtained from patients' archived files. Disease staging was performed according to the tumor, node, and metastasis (TNM) staging system. Progression-free survival (PFS) was defined as the time from diagnosis to progression.

Biomarker Assessment

EGFR mutation analysis was performed on the isolated DNA with an Easy PGX AriaDx real-time PCR device using an EasyPGX Ready EGFR mutation analysis kit prepared for EGFR. The exon

Fig. 1. Disposition of patients (CONSORT diagram).

18 codon 719 region, exon 19 deletions, exon 20 insertions and codon 768 and 790 regions, and exon 21 codon 858 and 861 regions of the EGFR gene were analyzed (85 possible mutation sites were examined). ALK positivity were assessed both by VENTANA ALK (D5F3) immunohistochemical assay and FISH using a Vysis ALK Break Apart FISH Probe kit (Abbott Molecular, Abbot Park, IL, USA). For ROS 1 assessment, a Vysis ROS 1 Break Apart 6q22 FISH Probe kit (Abbott Molecular) was used.

Statistical Methods

SPSS 15.0 for Windows was used for the statistical analysis. Descriptive statistics were given as a number and percentage for categorical variables, and the average, SD, and minimum and maximum for numerical variables. Comparisons of the numerical variables in 2 independent groups were made using the Mann-Whitney U test, since the normal distribution condition was not met. Comparisons of the ratios in the groups were made using the χ^2 test. The determinant factors were examined by Cox regression analysis, while a Kaplan-Meier survival analysis was performed. A statistical significance level of alpha was accepted as $p < 0.05$.

Results

Patient Characteristics

The study included 303 de novo metastatic NSCLC patients without a driver mutation, consisting of 260 (85.8%) males and 43 (14.2%) females. The mean age was 59.9 ± 11.1 years (range 21–92). Thirty-five (11.6%) patients had no history of smoking. Of the 303 patients, 132 (43.6%) had an ECOG performance scale (PS) of 2. The most common comorbidities were HT (17.5%), COPD (13.2%),

Table 1. Patient characteristics

Age at diagnosis, years	
Mean ± SD (min.–max.)	59.9±11.1 (21–92)
Gender	
Female	43 (14.2)
Male	260 (85.8)
Smoking history	
No	35 (11.6)
Yes	261 (86.1)
ECOG-PS	
0–1	171 (56.4)
2	132 (43.6)
Comorbidities	
HT	53 (17.5)
DM	8 (2.6)
CAD	8 (2.6)
COPD	40 (13.2)
Tumor histology	
NOS	80 (26.4)
SCC	96 (31.7)
AC	127 (41.9)
Grade	
2	147 (48.5)
3	156 (51.5)
Metastatic status at diagnosis	
Oligometastatic	206 (68.0)
Multiple	97 (32.0)
Site of metastasis	
Brain	121 (39.9)
Contralateral lung	73 (24.1)
Liver	65 (21.5)
Surrenal gland	90 (29.7)
Bone	148 (48.8)
Pleura	64 (21.1)
Others	31 (10.3)
DDC day	
Mean ± SD (min.–max.)	38.2±54.5 (0–501)
DDC group	
A	183 (60.4)
B	120 (39.6)
First-line CT regimen	
Platinum + pemetrexed	33 (10.9)
Platinum + paclitaxel	71 (23.4)
Platinum + docetaxel	57 (18.8)
Platinum + gemcitabine	107 (35.3)
Platinum + etoposide	4 (1.3)
Platinum + vinorelbine	31 (10.2)
Number of CT cycles	
Median (min.–max.)	4 (1–6)
Progression after CT	
No	7 (2.3)
Yes	296 (97.7)
Last status	
Alive	54 (17.8)
Dead	249 (82.2)

Data are presented as *n* (%), unless otherwise indicated. ECOG-PS, Eastern Cooperative Oncology Group performance scale; DDC, duration between diagnosis and the start of first-line chemotherapy; CT, chemotherapy; NOS, not otherwise specified; SCC, squamous cell carcinoma; AC, adenocarcinoma; HT, hypertension; DM, diabetes mellitus; CAD, coronary arter disease; COPD, chronic obstructive pulmonary disease.

DM (2.6%), and CAD (2.6%). The number of patients with AC, SCC, and NSCLC-NOS were 127 (41.9%), 96 (31.7%), and 80 (26.4%), respectively. Of the 303 patients, 156 (51.5%) had a poorly differentiated tumor. The number of patients with oligometastatic was 206 (68.0%). The most common sites of metastasis at diagnosis were as follows: brain (39.9%), contralateral lung (24.1%), liver (21.5%), surrenal glands (29.7%), bone (48.8%), pleura (21.1%), and other (10.2%). In the first-line treatment, all patients received platinum-based combination CT. The median number of CT cycles was 4.0 (range 1–6). During the median follow-up time of 10.0 months (range 1–48) disease progressed in 296 (97.7%) patients and 249 (82.2%) patients died. The mean DDC was calculated as 38.2 ± 54.5 days. The number of patients in group A and B were 183 (60.4%) and 120 (39.6%; Table 1).

Progression-Free Survival

The median PFS was 5.0 (95% CI 4.3–5.7) months in all patients. In the subgroup analysis, the median PFS in group A was 5.0 months (95% CI 4.1–5.9), whereas it was 6.0 months for group B (95% CI 4.9–7.1), indicating a statistically non-significant difference between the groups (log-rank *p* = 0.268; Fig. 2).

In the univariate Cox regression analysis for PFS, including ECOG-PS, pleural metastasis, and platinum + vinorelbine were factors that negatively affected PFS, whereas the number of CT cycles was the factor associated with favorable PFS (*p* < 0.001, *p* = 0.006, *p* = 0.039, and *p* < 0.001, respectively). Likewise, in the multivariate Cox regression analysis for PFS, including the number of CT cycles was the positive predictor of PFS, whereas ECOG-PS, bone metastasis, and pleural metastasis were associated with negatively affected PFS (*p* < 0.001, *p* = 0.006, *p* < 0.001, and *p* < 0.001, respectively; Table 2). There was no relation between DDC and PFS in the univariate or multivariate analysis.

Overall Survival

The median overall survival (OS) was 10.0 months (95% CI 8.8–11.2) in all patients. In the subgroup analysis, the median OS in group A was 10.0 months (95% CI 8.8–11.2), whereas for group B it was 11.0 months (95% CI 7.8–14.2), indicating a statistically non-significant difference between the groups (log-rank *p* = 0.341; Fig. 2).

Univariate Cox regression analysis for OS revealed that age at diagnosis, male gender, smoking history, ECOG-PS, poorly differentiated tumor, SCC histology, presence of multiple metastasis at diagnosis, metastasis to bone, and platinum + vinorelbine CT were the negative predictors of OS, whereas AC histology, receiving platinum + pemetrexed CT, and the number of CT cycles were the positive factors associated with OS (*p* = 0.006, *p* = 0.019, *p* = 0.004, *p* < 0.001, *p* = 0.010, *p* = 0.042, *p* = 0.006,

Fig. 2. Median PFS (A, C) and median OS (B, D) in all patients (A, B) and in the groups (C, D).

$p = 0.005$, $p < 0.001$, $p = 0.002$, $p < 0.001$, and $p < 0.001$, respectively). In the multivariate Cox regression analysis, age at diagnosis, smoking history, ECOG-PS, HT, poorly differentiated tumor, and metastasis to bone were the negative predictors of OS, whereas the number of CT cycles in the first-line setting was found to be a positive predictor of OS ($p = 0.022$, $p = 0.046$, $p = 0.010$, $p = 0.029$, $p = 0.032$, $p = 0.027$, and $p < 0.001$, respectively; Table 3). There was no relation between DDC and OS in the univariate or multivariate analysis.

Discussion

In this study, the prognostic impact of DDC in NSCLC patients without a driver mutation was investigated. It was demonstrated that DDC was not associated with PFS

and OS, nor was there a difference between group A and group B in terms of PFS and OS.

There are some studies in the literature focused on the optimal time to initiate CT, mostly in an adjuvant setting. The survival benefit of adjuvant CT was shown to be time dependent, and studies have also reported that delayed CT might be associated with poor patient and disease characteristics, as well as with an increase in comorbidity in breast cancer and colorectal cancer [19–22]. Studies with similar results may cause anxiety about the waiting period in physicians and patients. For these reasons, some patients receive CT before their test results.

In a study assessing the real-world ALK testing patterns among community practices, it was found that the median time from advanced disease diagnosis to ALK test results was 29 days, and that the proportion of patients who started CT before receiving ALK test results was 21.5%. There

Table 2. Factors affecting PFS

	Univariate analysis for PFS			Multivariate analysis for PFS		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age at diagnosis						
Years	0.999	0.988–1.009	0.788			
Gender						
Male vs. female	1.070	0.768–1.490	0.689			
Smoking history						
Yes vs. no	1.106	0.762–1.607	0.596			
ECOG						
2 vs. 0–1	2.330	1.812–2.995	<0.001	1.953	1.487–2.563	<0.001
Comorbidities						
HT	0.804	0.591–1.094	0.164	1.095	0.784–1.529	0.594
DM	0.537	0.253–1.14	0.105	0.697	0.322–1.509	0.360
CAD	0.817	0.386–1.732	0.598			
COPD	0.618	0.198–1.929	0.407			
Grade						
3 vs. 2	1.429	0.626–3.265	0.397			
Tumor histology						
NOS	0.972	0.741–1.275	0.837			
SCC	0.995	0.779–1.272	0.969			
AC	0.979	0.775–1.236	0.857			
Metastatic status						
Multiple vs. oligo	1.138	0.889–1.457	0.305			
Site of metastasis						
Brain	0.850	0.672–1.075	0.176	0.902	0.694–1.173	0.442
Contralateral lung	0.915	0.698–1.199	0.519			
Liver	0.999	0.757–1.318	0.994			
Surrenal gland	0.897	0.697–1.153	0.395			
Bone	1.245	0.989–1.568	0.062	1.423	1.107–1.830	0.006
Pleura	1.481	1.118–1.962	0.006	1.910	1.400–2.605	<0.001
Others	1.210	0.829–1.768	0.323			
DDC						
Days	0.998	0.996–1.000	0.083			
DDC						
≤30 vs. >30 days	0.883	0.698–1.116	0.298	0.854	0.655–1.114	0.245
CT regimen (platinum +)						
Pemetrexed	0.828	0.567–1.209	0.329			
Paclitaxel	1.200	0.914–1.576	0.190	1.099	0.775–1.557	0.597
Docetaxel	1.076	0.799–1.449	0.630			
Gemcitabine	0.797	0.627–1.014	0.064	0.888	0.660–1.195	0.432
Etoposide	0.934	0.347–2.510	0.892			
Vinorelbine	1.491	1.020–2.179	0.039	1.149	0.741–1.782	0.535
Number of CT cycles	0.731	0.672–0.795	<0.001	0.727	0.660–0.800	<0.001

Please refer to Table 1 footnote for definitions of abbreviations. Bold values are statistically significant.

was no information, however, about the mutation status of patients receiving CT before test results and the prognostic impact of early CT [18]. Similarly, in a trial published by Lim et al. [23], a total of 175 advanced non-squamous NSCLC patients who were tested for EGFR and ALK were included. Among these patients, 19% of those with positive test results had received CT before targeted therapy. In another study including ALK and advanced NSCLC patients, it was evaluated whether receiving CT before initiation of an ALK inhibitor affects survival and it was found that patients had similar survival outcomes

regardless of whether they received CT before initiation of ALK inhibitor treatment [24]. The studies presented above, however, did not compare early or delayed CT in NSCLC patients without a driver mutation.

Only patients without driver mutations were included in the present study, which evaluated whether DDC affects PFS and OS, and which demonstrated that DDC was associated with neither. Also, patients were grouped according to DDC as ≤30 and >30 days and observed that there was no difference between groups in terms of PFS and OS. Results may be associated with a relatively higher

Table 3. Factors affecting OS

	Univariate analysis for OS			Multivariate analysis for OS		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age at diagnosis						
Years	1.016	1.004–1.027	0.006	1.038	1.005–1.071	0.022
Gender						
Male vs. female	1.580	1.078–2.317	0.019	1.306	0.487–3.508	0.596
Smoking history						
Yes vs. no	1.981	1.250–3.140	0.004	2.959	1.018–8.599	0.046
ECOG						
2 vs. 0–1	3.743	2.804–4.997	<0.001	3.083	1.305–7.285	0.010
Comorbidities						
HT	0.785	0.555–1.109	0.169	1.979	1.072–3.651	0.029
DM	0.602	0.267–1.357	0.221	2.014	0.687–5.905	0.202
CAD	1.160	0.515–2.612				
COPD	1.174	0.376–3.671				
Grade						
3 vs. 2	3.062	1.306–7.179	0.010	3.539	1.115–11.22	0.032
Tumor histology						
NOS	1.246	0.938–1.655	0.130	1.689	0.184–15.46	0.643
SCC	1.313	1.010–1.707	0.042	1.597	0.183–13.92	0.672
AC	0.663	0.512–0.589	0.002	1.808	0.210–15.55	0.590
Metastatic status						
Multiple vs. oligo	1.446	1.112–1.880	0.006	0.342	0.094–1.246	0.104
Site of metastasis						
Brain	0.831	0.644–1.074	0.157	0.902	0.456–1.782	0.767
Contralateral lung	0.871	0.649–1.169	0.357			
Liver	0.932	0.688–1.263	0.650			
Surrenal gland	1.007	0.769–1.318	0.959			
Bone	1.433	1.115–1.843	0.005	1.885	1.073–3.311	0.027
Pleura	1.093	0.804–1.484	0.570			
Others	1.458	0.989–2.149	0.057	1.170	0.136–10.05	0.886
DDC						
Days	0.998	0.995–1.000	0.080			
DDC						
≤30 vs. >30 days	0.886	0.686–1.145	0.356	0.922	0.512–1.661	0.788
CT regimen (platinum +)						
Pemetrexed	0.272	0.144–0.513	<0.001	0.507	0.116–2.211	0.366
Paclitaxel	1.241	0.926–1.661	0.148	1.296	0.643–2.611	0.468
Docetaxel	1.144	0.842–1.556	0.390			
Gemcitabine	0.875	0.675–1.134	0.313			
Etoposide	1.637	0.608–4.409	0.329			
Vinorelbine	2.109	1.436–3.097	<0.001	1.241	0.434–3.542	0.687
Number of CT cycles	0.600	0.547–0.660	<0.001	0.680	0.537–0.860	0.001

Please refer to Table 1 footnote for definitions of abbreviations. Bold values are statistically significant.

tumor doubling time in NSCLC patients than the mean DDC (38.2 ± 54.5 days). In a study published in 2014, it was found that the median TDT was 139 days [25]. In another trial, the median tumor doubling time of the solid component of the tumor was calculated as 175.5 days [26].

The present study has a few limitations. First, it was planned retrospectively. Therefore, there was no balancing of patient characteristics between the groups. Second, although the study included a statistically sufficient number of patients, that number could have been higher. Also, we could not evaluate whether or not DDC affected the

prognosis of patients treated with an immunotherapy and CT combination. However, this is the first study focused on the prognostic impact of DDC in metastatic NSCLC patients without driver mutations.

Conclusion

Our results show that higher DDC was not associated with a worse prognosis in metastatic NSCLC patients without driver mutations. Furthermore, earlier studies

demonstrated that early CT without additional improvement in patients with a positive test result may result in additional side effects and cost. In this context, it is safer for patients and their physicians to wait for test results before starting CT. However, these results need to be supported by prospective randomized controlled trials.

Statement of Ethics

The study was performed in accordance with the Declaration of Helsinki. The patients gave their written informed consent before the study. Both patient consent and the approval of the Health Sciences University, Okmeydanı Training and Research Hospital Ethics Committee were received.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

S.A., A.S., S.C., N.Y., and R.C., planning. S.A., R.C., S.C., N.Y., and S.S., data collection. A.S., S.A., and R.C., statistical analysis.