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The Effect of Chemotherapeutic Agents on Survival in Metastatic Non-Small-Cell Lung Cancer with KRAS Mutation

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Abstract

Introduction *KRAS* mutation is observed in up to 30% of non-small-cell lung cancer (NSCLC) cases and is corelated with a poor prognosis. In the cases with *KRAS* p.G12C mutation and first-line chemotherapy (± immunotherapy) resistance, a targeted drug option is available.

Objectives Our study aimed to examine the correlation between first-line chemotherapy agents and treatment response in patients with KRAS-mutated metastatic NSCLC.

Materials and Methods Retrospective database searches were performed on cases diagnosed with metastatic NSCLC at our center between January 2019 and December 2021 that were found to be KRAS mutation positive using the *next-generation sequencing* (NGS) approach. The cases were classified into five subgroups based on the chemotherapy regimens (platinum + gemcitabine, platinum + taxane, platinum + pemetrexed, platinum + vinorelbine, and others). The clinical and demographic data of 41 cases were analyzed retrospectively, and survival analyses were performed using the Kaplan–Meier method.

Results Thirty-seven of 41 patients (90.2%) were males, and 27 (65.9%) had adenocarcinoma histology. The most prevalent mutation was KRAS G12C, with 12 cases (29.2%), followed by KRAS G12V, with 9 cases (21.9%). Other mutations were as follows: KRAS G12D 4 (9%), KRAS G13C 3 (7.3%), KRAS G12A 2 (4.8%), KRAS G12R 2 (4.8%), KRAS Q61H 2 (4.8%), KRAS Q61L 2 (4.8%), KRAS V14I 2 (4.8%), KRAS A146T 1 (2.4%), KRAS G13G 1 (2.4%), and KRAS G1C 1 (2.4%). The median progression-free survival (mPFS) for all groups was 4.6 months (95% confidence interval [CI]: 2.7-6.5), and there were no statistically significant differences between the groups ($p = 0.121$). The median overall survival (mOS) for all groups was 9.3 months (95% CI: 3.8–14.5), and there were no statistically significant differences between the groups ($p = 0.805$).

Keywords
- metastatic NSCLC
- KRAS
- chemotherapy
- OS
- PFS
- platinum

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Conclusions OS and PFS analyses showed no differences between platinum + taxane, platin + pemetrexed, platinum + gemcitabine, and platin + vinorelbine used in first-line treatments for KRAS mutant NSCLC cases. We believe that patient-specific characteristics may be a determining factor in selecting chemotherapy for this patient population.

Introduction

Lung cancer causes approximately 1.8 million deaths annually worldwide.[1] Despite the increase in screening programs, the improvement of surgical techniques, and the use of targeted therapies and immunotherapies, lung cancer is the most common cause of cancer-related death.[2,3] The disease stage is the most significant indicator of prognosis, with 5-year survival rates less than 10%.

Before selecting a course of treatment in metastatic cases, it is recommended that ALK and ROS 1 rearrangement, BRAF V600E mutation, EGFR mutation, HER2 mutation, KRAS mutation, METex14 mutation, NTRK gene fusion, and RET rearrangement, programmed death ligand 1 (PDL-1) expression be analyzed as predictive biomarkers in treatment.[4]

The RAS oncogene family includes the *KRAS*, *NRAS*, and *HRAS*. KRAS is a G-protein in MAP/ERK pathway with GTPase activity. In the activated KRAS mutation, intracellular signaling pathways are activated. It is observed in up to 30% of NSCLC cases, primarily in adenocarcinoma subtypes. Mutations are frequently detected at codons 12, 13, 61.[5–7] The presence of the KRAS oncogene is related to a poor prognosis and unresponsiveness to EGFR *tyrosine kinase inhibitors* treatment.[8–10] Sotorasib is a Food and Drug Administration (FDA) approved treatment option for cases with the KRAS p.G12C mutation that were diagnosed with non-small-cell lung cancer (NSCLC). Sotorasib is recommended by the National Comprehensive Cancer Network (NCCN) guideline version 5.2022 as a treatment option in metastatic cases unresponsive to platinum-based chemotherapy (± immunotherapy).[11] There are cell culture and clinical studies revealing that KRAS mutations may play role in the treatment of NSCLC cases.[5,12] In metastatic NSCLC patients with KRAS mutation, targeted therapies are used in those who have progressed after first-line chemotherapy. Systemic chemotherapy in first-line treatment still maintains its importance today. There are different chemotherapy protocols that can be used in metastatic NSCLC patients. In our study, we aimed to investigate the chemotherapeutic agents used in metastatic NSCLC patient with KRAS mutation and whether there is a relationship between these agents and survival.

Materials and Methods

Patients

Patients with metastatic NSCLC with KRAS mutation diagnosed and followed up in our center, between January 2019 and December 2021, were evaluated retrospectively. The data of the patients accessed through the hospital electronic automation system and patient files were recorded. Patient demographics, histopathological features, disease stage at diagnosis, next-generation sequencing (NGS) test results, PDL-1 levels, palliative treatment history, chemotherapy protocols, date of diagnosis, date of progression, and date of death were recorded.

Inclusion Criteria

The inclusion criteria were determined as follows: being older than 18, not having received chemotherapy in the past, being diagnosed with metastatic disease, not having undergone curative radiotherapy or surgery, and not having a positive driver mutation.

Exclusion Criteria

The exclusion criteria were determined as follows: patients with unknown mutation status, patients with positive EGFR or ALK mutations, patients with no follow-up data, patients without metastatic stage, patients who underwent curative radiotherapy, and surgical treatment. A total of 667 lung cancer cases were evaluated with the NGS technique; RAS mutation was detected in 66 patients. After applying the inclusion and exclusion criteria, the data of 41 cases were analyzed in total. Parameters for progression-free survival (PFS) and overall survival (OS) were generated based on the clinical and demographic characteristics and chemotherapeutic agents employed in the treatment. The platinum group of chemotherapeutic medicines consisted of carboplatin and cisplatin, and the taxane group of medicines consisted of docetaxel and paclitaxel. The primary endpoint of the study was to explore the relationship between chemotherapy protocols and OS and PFS. The secondary endpoint was to explore the mutation subtypes of the patient population and the chemotherapy options preferred in patients. For KRAS mutation analysis, the QIAseq Solid Tumor Custom Panel was utilized, and somatic mutation analyses were conducted by performing mutation studies in genes using the NGS method.

Statistical Method

The cases were classified into five subgroups based on the chemotherapy regimens they received: platinum + gemcitabine, platinum + taxane, platinum + pemetrexed, platinum + vinorelbine, and others. In the survival analyses for these subgroups, the Kaplan–Meier analysis was performed. Statistical significance was accepted as $p < 0.05$.

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Table 1 Demographic and clinical characteristics of cases

Variable		*n* (%)
Gender	Female	4 (9.8)
	Male	37 (90.2)
Age (y), mean (minimum–maximum)		65.2 (47–81)
Histology	Adenocarcinoma	27 (65.9)
	Squamous	4 (9.8)
	NOS	10 (24.4)
Stage	4	41 (100)
Performance status pretreatment	ECOG 0	6 (14.6)
	ECOG 1	9 (21.9)
	ECOG 2	26 (63.5)
	ECOG 3	0 (0)
	ECOG 4	0 (0)
KRAS mutation	KRAS G12C	12 (29.2)
	KRAS G12V	9 (21.9)
	KRAS G12D	4 (9)
	KRAS G13C	3 (7.3)
	KRAS G12A	2 (4.8)
	KRAS G12R	2 (4.8)
	KRAS Q61H	2 (4.8)
	KRAS Q61L	2 (4.8)
	KRAS V14I	2 (4.8)
	KRAS A146T	1 (2.4)
	KRAS G13G	1 (2.4)
	KRAS G1C	1 (2.4)
Other common mutations	BRCA-1	7 (17)
	BRCA-2	5 (12)
	TP53	2 (4.8)
	BRAF V600E	1 (2,4)
	NTRK 1	2 (4.8)
	PIK3CA	2 (4.8)
	PTEN	1 (2,4)
	MET amplification	3 (7.3)
Metastasis site	Liver	6 (14.6)
	Lung	9 (21.9)
	Brain	6 14.6)
	Bone	14 (34.1)
	Adrenal gland	9 (21.9)
NGS studied tissue	Lung	18 (51.4)
	Lymph node	3 (8.6)
	Blood	4 (11.4)
	Brain	3 (8.6)
	Bone	4 (11.4)
	Adrenal gland	2 (5.7)

(*Continued*)

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Table 1 (*Continued*)

Variable		*n* (%)
	Pleura	2 (5.7)
PDL-1 staining (mean)		16.4 (0–97)
Palliative surgery		1 (2.4)
Palliative radiotherapy		13 (31.7)
Chemotherapy protocols	Platinum + taxane	24 (58)
	Platinum + pemetrexed	6 (14.6)
	Platinum + gemcitabine	4 (9.7)
	Platinum + vinorelbine	3 (7.3)
	Platinum	2 (4.9)
	Taxane	1 (2.4)
	Vinorelbine	1 (2.4)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma; NGS, next-generation sequencing; NOS, not otherwise specified; PDL-1, Programmed death-ligand 1.

Ethics

Karadeniz Technical University (KTU) Faculty of Medicine Ethics Committee (April 29, 2022, numbered 24237859-323) approved the study. All stages of our work were carried out in accordance with the 1964 Helsinki Declaration and its later amendments. Since our study was retrospective, the ethics committee did not request informed consent from the subjects.

Results

The data from 41 cases with metastatic NSCLC who tested positive for the KRAS mutation were analyzed retrospectively. The study population included of 37 males (90.2%) and 4 females (9.8%). The mean age of the patients was 65.2 (47–81 years). Histologically, adenocarcinoma was the most prevalent kind at 27 (65.9%) cases, followed by squamous with 4 (9.8%) cases and NOS with 10 (24.4%) cases. All cases had a metastatic disease at diagnosis. KRAS mutation locations were detected as follows: KRAS G12C in 12 (29.2%) cases, KRAS G12V in 9 (21.9%) cases, KRAS G12D in 4 (9%) cases, KRAS G13C in 3 (7.3%) cases, KRAS G12A in 2 (4.8%) cases, KRAS G12R in 2 (4.8%) cases, KRAS Q61H in 2 (4.8%) cases, KRAS Q61L in 2 (4.8%) cases, KRAS V14I in 2 (4.8%) cases, KRAS A146T in 1 (2.4%) case, KRAS G13G in 1 (2.4%) case, and KRAS G1C in 1 (2.4%) case. In nearly half of the cases (51.4%), the NGS test was performed on lung tissue. Chemotherapy preferences were as follows: platinum + taxane in 24 (58%) cases, platinum + pemetrexed in 6 (14.6%) cases, platinum + gemcitabine in 4 (9.7%) cases, platinum + vinorelbine in 3 (7.3%) cases, platinum in 2 (4.9%) cases, taxane in 1 (2.4%) case, and vinorelbine in 1 (2.4%) case.

Demographic and clinical data of the cases are presented in ►**Table 1**. The mean OS (mOS) at 95% confidence interval (CI) was determined as 8.9 months (6.2–11.5) for the platinum + taxane group, as 5.4 months (–) for the platinum + pemetrexed group, as 14.3 months (3.2–25.3) for the platinum + gemcitabine group, as 19.2 months (–) for the platinum + vinorelbine group, and as 8.4 months (0–17.9) in other cases. The overall mOS was 9.3 months (3.8–14.5) in all groups at 95% CI, and there was no statistically significant difference in the mOS values between the groups ($p = 0.805$). The mean PFS (mPFS) at 95% CI was determined as 3.5 (1–5.9) for the platinum + taxane group, as 1.3 (0–3.0) for the platinum + pemetrexed group, as 8.0 (1.8–14.2) for the platinum + gemcitabine group, as 10.5 (0–27) for the platinum + vinorelbine group, and as 2.1 (0.7–3.4) in other cases. The overall mPFS for all groups was 4.6 (2.7–6.5) at 95% CI, and there was no statistically significant difference in the mPFS values between the groups ($p = 0.121$; ►**Table 2**). ►**Fig. 1** depicts the OS Kaplan–Meier curve, while ►**Fig. 2** depicts the PFS curve.

Discussion

In treating metastatic NSCLC, the level of PDL-1, the existence of driver mutations, the number of metastatic sites, histological subtype, tumor load, and rate of disease progression serve as a guide for clinicians. Due to the survival benefits of targeted agents and immunotherapy, molecular tests for driver mutations and screening for immunological biomarkers are recommended in all cases by the guidelines.[13–15]

In the cases with no mutation that can be treated with targeted therapy in metastatic NSCLC, treatment with a combination of chemotherapy and immunotherapy or immunotherapy alone may be considered.[16,17] There are different alternative combination treatments available in chemotherapy options. Chemotherapy regimens based on platinum have been revealed to be superior to those based on platinum-free chemotherapy. The effectiveness of pemetrexed in nonsquamous histology is well established.[18,19] Moreover, it has been established that the addition of bevacizumab to doublet platinum-based regimens significantly improves OS and PFS.[20]

KRAS is the most common mutation and more prevalent in smokers with NSCLC. It causes mutations in codon 12 most

Table 2 The relationship between chemotherapy and OS-PFS

Chemotherapy protocols, *n* (%)	Median OS, mo (95% CI)	Median PFS, mo (95% CI)
Platinum + taxane: 24 (58)	8.9 (6.2–11.5)	3.5 (1.0–5.9)
Platinum + pemetrexed: 6 (14.6)	5.4 (–)	1.3 (0–3.0)
Platinum + gemcitabine: 4 (9.7)	14.3 (3.2–25.3)	8.0 (1.8–14.2)
Platinum + vinorelbine: 3 (7.3)	19.2 (–)	10.5 (0–27)
Others: 4 (9.7)	8.4 (0–17.9)	2.1 (0.7–3.4)
Overall	9.3 (3.8–14.5)	4.6 (2.7–6.5)
Log-rank test (*p*)	0.805	0.121

Abbreviations: CI: confidence interval; OS: overall survival; PFS: progression-free survival.

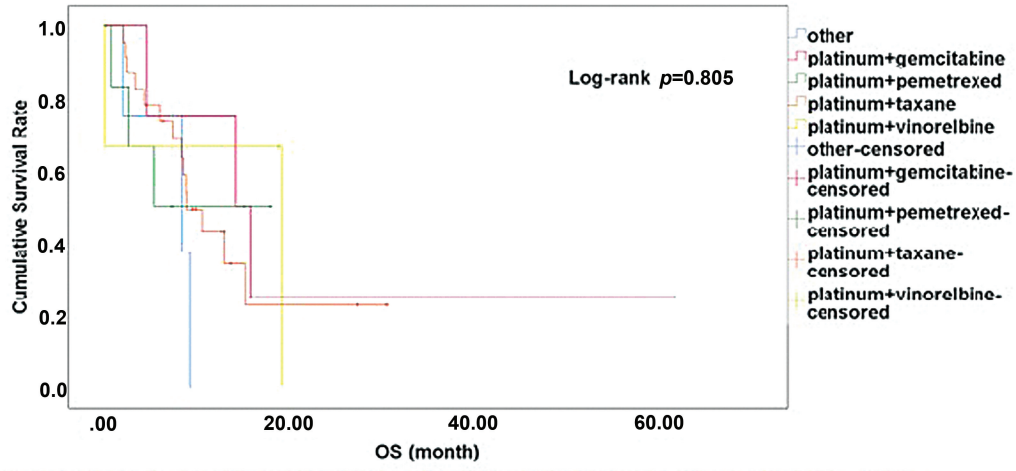

Fig. 1 The Kaplan–Meier curve shows the relationship between chemotherapy and overall survival (OS).

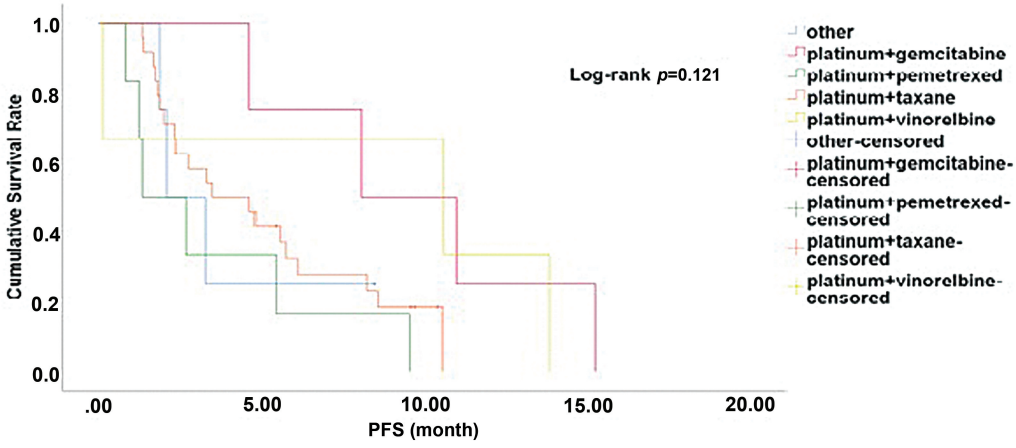

Fig. 2 The Kaplan–Meier curve shows the relationship between chemotherapy and progression-free survival (PFS).

frequently (95%), and mutations occur in the G12C, G12V, and G12D loci, in that order.[21,22] This mutation has been found to have a negative effect on survival in patients with NSCLC treated with platinum-based regimens.[23] Advanced NSCLC patients with KRAS p.G12C mutation and prior chemotherapy ± immunotherapy had an mPFS of 6.8 months (95% CI: 5.1–8.2) and an mOS of 12.5 months (95% CI: 10.0–could not be evaluated) had with the use of Sotorasib.[11] In a separate study, it was found that 39 KRAS mutant NSCLC cases caused a numerical decrease in OS and PFS when compared to 69 KRAS wild NSCLC cases. While the difference in survival was not significant, it was observed that the frequency of aggressive disease course and liver and brain metastases increased.[24]

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In light of the current data, the aim of our study was to explore the contribution of chemotherapy selection to survival of all patients with a KRAS mutation in the first-line chemotherapy selection, given that guidelines only recommend the use of a KRAS inhibitor in cases involving a KRAS G12C mutation in the second-line treatment.

In a multicenter study involving 464 cases of stage 3B and 4 NSCLC cases with a KRAS mutation, the mutation frequency was G12C (46%), G12V (20%), and G12D (10%), respectively. The PFS was statistically substantially longer in the platinum + taxane treatment group than in the platinum + pemetrexed or gemcitabine groups. In this study, the subgroup G12V is identified as the source of the difference. On the other hand, there was no difference in OS between chemotherapy regimens and KRAS mutation subgroups. In the study population, more than half of the patients in the platinum + taxane group received bevacizumab. The survival effect of adding bevacizumab to treatment has been demonstrated, and we think that the contribution to PFS could be attributable to bevacizumab.[12] The difference of our study is that there is a platinum + vinorelbine subgroup within the chemotherapy groups and we did not have a case involving the use of biological agents. Therefore, we believe the correlation between KRAS mutations and conventional chemotherapy combinations can be evaluated with more precision.

In a study examining 99 NSCLC cases, which is one of the first preclinical studies on drug sensitivity and tumor behavior of distinct KRAS mutations, it was revealed that the most prevalent mutations were G12C (39%), G12V (21.8%, G12D (15.5%). The three most frequently detected tumor clones were replicated to investigate the chemotherapy sensitivity. G12C-mutated tumor clones exhibited decreased sensitivity to cisplatin and increased sensitivity to taxane and pemetrexed. Moreover, the G12V clone was more resistant to pemetrexed and more sensitive to cisplatin.[5] This distribution is consistent with the frequency of mutations identified in our study population. Due to the inability to perform a submutation analysis on our cases, we could not comment on the chemotherapy response according to the KRAS subgroups.

Conclusion

In conclusion, there was no statistically significant difference in survival between platinum + taxane, platin + pemetrexed, platin + gemcitabine, and platin + vinorelbine that were used in the first-line chemotherapy of metastatic NSCLC cases with a KRAS mutation. Patient-specific characteristics, drug side effects, and patient preferences may be a determining factor in selecting chemotherapy for NSCLC cases with a KRAS mutation. The primary limitation of our study was our inability to analyze the effect of chemotherapy options based on the number of cases in the KRAS subgroups. Another limitation of our study is the limited number of patients treated with immunotherapy as first-line treatment. We believe our study will serve as a source for future research that will include more case groups and incorporate the combinations of chemotherapy and immunotherapy. Our study is the first to report the efficacy of chemotherapy in cases of KRAS mutant metastatic NSCLC in our country and at our institution.

Author Contributions

Mustafa Emre Duygulu was responsible for design, statistical analysis, and manuscript preparation. Data analysis was done by Atila Yildirim. Literature search was conducted by Eyyup Ayas. Data acquisition was done by Nese Alyildiz. Definition of intellectual content was provided by Sevdegul Aydin Mungan. Manuscript editing and manuscript review were done by Evren Fidan. All the authors read and approved the final version of the manuscript.

Patient Consent

None declared.

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None.

Conflict of Interest

None declared

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