CASE REPORT

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Yazışma Adresi
Correspondence Address

Onur Yazdan BALCIK
Department of Medical Oncology, Adnan Menderes University, Aydın, Turkey
yazdanbalcik@hotmail.com

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Onur Yazdan BALCIK
Department of Medical Oncology, Adnan Menderes University, Aydın, Turkey
ORCID ID: 0000-0002-3386-2075

Esin OKTAY
Department of Medical Oncology, Adnan Menderes University, Aydın,Turkey
ORCID ID: 0000- 0002-5974-6339

Gizem DONMEZ YALCIN
Department of Medical Bıology, Adnan Menderes University, Aydın,Turkey
ORCID ID: 0000-0002-5121-8232

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Which Treatment Should Be Selected for the Optimum Approach to Patients with Non-small Cell Lung Cancer with More than Driver Mutations? A Case Report and Literature Review

Birden Fazla Sürücü Mutasyonlu Küçük Hücre Olmayan Akciğer Kanserli Hastalarda Optimum Yaklaşım İçin Hangi Tedavi Seçilmelidir? Bir Vaka Raporu ve Literatür İncelemesi

ABSTRACT
We present a case of concomitant c-ros oncogene 1 (ROS1) and anaplastic lymphoma kinase (ALK) and fusion in nonsmall cell lung cancer (NSCLC) in a 59-year-old patient and review the treatment efficacy of co-mutations. The choice of the treatment and its effectiveness with rare co-mutations is a subject of considerable interest. This review will provide clues to the optimal treatment approach to NSCLC patients with more than one driver mutation. However, randomized studies are needed to clarify which patients with concurrent mutations may benefit from chemotherapy or related tki.

Key Words:
Lung, Mutation, Alk, Ros

ÖZ
Ellidokuz yaşındaki bir hastada küçük hücreli olmayan akciğer kanserinde (KHDAK) bir anaplastik lenfoma kinaz (ALK) ve c-rosonkogen 1 (ROS1) füzyonu vakasını sunuyoruz ve ko-mutasyonların tedavi etkinliğini gözden geçiriyoruz. Tedavinin seçimi ve nadir ko-mutasyonlarla etkinliği oldukça ilgi çeken bir konudur. Bu derleme, birden fazla sürücü mutasyonu olan KHDAK hastalarına optimal tedavi yaklaşımına dair ipuçları sağlayacaktır. Bununla birlikte, hangi hastaların uygun TKI veya kemoterapiden fayda görebileceğini netleştirmek için randomize çalışmalara ihtiyaç vardır.

Anahtar Kelimeler:
Akciğer, Mutasyon, Alk, Ros

INTRODUCTION
The majority of patients with non-small cell lung cancer (NSCLC) are in the advanced stage of the disease at the time of initial diagnosis. Chemotherapy has been the most important treatment approach for the last three decades, but it has only limited effectiveness. Treatment approaches for NSCLC with molecular targets have come into common use with promising results compared to chemotherapy alone (1-4). Large randomized and controlled trials have consistently demonstrated that target therapies are more effective than cytotoxic chemotherapy.
Epidermal growth factor receptor (EGFR) mutations are the most common molecular changes. In addition, c-ros oncogene 1 (ROS1) and anaplastic lymphoma kinase (ALK) represent two

rearrangement genes and these rearrangements are observed less frequently than EGFR mutations in NSCLC. Many studies have shown that the percentage of EGFR mutations, ALK rearrangements and ROS1 oncogene were observed approximately 10-28%, 3–7% and 1–2% respectively (5-8). NSCLCs that harbor these molecular targets are sensitive to treatment with tyrosine kinase inhibitors, and recent studies have shown-progression-free survival to be more than 18 months in EGFR mutant patients, 34 months in ALK rearrangement positive patients and 19 months in ROS1 rearrangement positive patients (9-11).

In NSCLC, genomic fusions and mutations are exclusive with respect to each other. Furthermore there are several recent studies showing that target genes may occur at the same time. Although most of these studies focus on EGFR mutations, there is little data on the frequency of ROS1/ALK coexistence (0.001%) (8-12).

There is a lack of information on whether the coexistence of EGFR/ALK/ROS1 has advantages over positivity alone, or whether this coexistence decreases the effectiveness of treatment. The choice of the treatment and its effectiveness with rare co-mutations is a subject of considerable interest. A review of literature identified only a few case reports to date addressing this issue. Our aim in the present study is to contribute to literature by reporting this rare condition, describing the prognosis of a patient in which a positive ALK/ROS1 rearrangement was detected. We further present a review of previously reported cases and related literature on EGFR/ALK/ROS1 coexistences and the applied treatment strategies. The treatment algorithm according to the mutation pair is also shown at table I.

Tablo I: Treatment algorithm according to mutation pair.

Mutation	Co-Mutation	Treatment	References
EGFR	ALK	FIRST LINE ANTI –ALK THERAPY	15
		SECOND LINE ANTI-EGFR THERAPY	16
	ROS	ANTI-EGFR THERAPY	19-20
ALK	ROS	CRIZOTINIB REZISTANCE CHEMOTERAPY	22
	K-RAS	CRIZOTINIB REZISTANCE CHEMOTERAPY	16-17
ROS	Tropomyosin 3	CRIZOTINIB	17
	Ezrin		
	CD74		
	Syndecan 4		

(Alk: Anaplastic Lymphoma Kinase, Co: Coincidence, Egfr: Epidermal Growth factor)

This study will provide clues to the optimal treatment approach to NSCLC patients with more than one driver mutations.

CASE REPORT

A 59-year-old male with an existing smoking history of 50 pack/year was admitted to hospital with a cough complaint, shortness of breath and weight loss. A lthough he was treated for pneumonia, he did not improve. A thorax computerized tomography (CT) revealed a 54-mm hilar region in the left lung and multiple 10-mm mediastinal lymphadenopathies. The mass had involved the pulmonary artery, and the patient had also chronic obstructive pulmonary disease. A pathological examination of specimens obtained via a trans-bronchial biopsy from the left lung hilar mass revealed adenocarcinoma, which was determined to be Grade 3. The patient underwent three cycles of chemotherapy with carboplatin (5AUC) and a paclitaxel (175mg/m2) regimen. Although the mass decreased to 36 mm, the pulmonary artery involvement rendered the patient inoperable. Consequently, three further cycles of the same regimen were applied.

A new pleural effusion developed in the left hemithorax, and the size of the mass was seen to increase to 38 mm on thorax CT. A cytology examination of a pleural effusion sample indicated malignancy. The patient was then treated with two cycles of cisplatin (70 mg/m2) and pemetrexed (500 mg/m2) however chemotherapy was reduced due to the neuropathic side effects. Upon re-evaluation, no change was noted in the size of the mass or lymph nodes, while the amount of pleural effusion increased. No mutation in EGFR gene was found ALK and ROS gene mutations were analyzed with fluorescent in situ hybridization, and ALK/ROS1 was found dually positive (15 cells out of 100 cells were found to be positive for ALK and 22 cells out of 100 cells were detected to be positive for Ros-1). The patient was treated immediately with 250 mg crizotinib for 3 months, 3 more cycles were given after partial response was seen.

The patient experienced no side effects. The size of the primary mass was constant after 7 months of crizotinib treatment. However, new metastatic masses developed in the contralateral lung, and a subcarinal 2cm lymph node occurred concurrently. Simultaneously, the amount of pleural effusion on the left increased, and a new pleural effusion developed on the right. The patient displayed shortness of breath, cough, fever, and finally was hospitalized with pneumonia. A COVID-19 PCR test was conducted and found to be negative. Additionally, a CT scan excluded COVD-19 possibility. The patient received pneumonia treatment, but died due to respiratory failure 3 days later.

DISCUSSION

NSCLCs are heterogeneous tumors and involve more than one oncogenic pathway. Patients with ROS1 fusions generally do not have ALK fusions, KRAS and EGFR mutations (13). However, some studies have shown that there may be driver genes that may accompany EFGR mutation. Information on mutations to accompany ALK and ROS1 rearrangements are limited (14).

EML4-ALK fusion and EGFR mutations were seen together in 0-8% of patients in a single study. A concomitant mutation in the EGFR (3 cases) or KRAS (5 cases) genes was observed in 19% of patients with ALK-positive lung adenocarcinoma. In

addition, in two patients with EGFR mutants, crizotinib response was better than erlotinib and two patients with KRAS mutant reported opposite responses to crizotinib. The study provided no information on the PFS of patients who responded to crizotinib (15). In another study, among 14 patients with adenocarcinoma, co-changes of ALK/KRAS were seen in nine patients and ALK/EGFR in five patients. In some studies, resistance to ALK-based TKI therapy was seen in concurrent KRAS/ALK mutations. Two of the patients with EGFR/ALK co-changes had a partial response for 5.7 and 7.3 months, while one had progressed immediately after 1.3 months of crizotinib use. In addition, three out of four patients with ALK/EGFR co-changes had to receive different EGFR TKI treatments after being treated with one EGFR TKI. A partial response was seen in one of four patients with osimertinib and three with afatinib. One patient achieved a complete response with osimertinib and one patient progressed immediately with erlotinib. With a first EGFR TKI treatment median PFS during treatment was 5.8 months (range 3.0–6.9 months). In the current study, patients with EGFR/ALK co-changes had worse outcomes with their EGFR and ALK TKIs than patients with both changes alone (16).

Our literature search has identified 15 ROS1 fusion partner genes in NSCLC (4). The most frequently occurring fusion partners include differentiation clusters tropomyosin 3 (TPM3), ezrin (EZR), CD74, syndecan 4 (SDC4). In a study, patients with various ROS1 fusion partners found no significant overall survival (OS) or progression-free survival (PFS) and demonstrated comparable efficacy to crizotinib in these patients. The median PFS could not be determined for the entire study group, but the median PFS was 258 days for patients with SDC4-ROS1 versus 357 days for those with other fusion partners (p=0.98 for OS; p=0.24 for PFS) (17).

ROS1 rearrangements are rarely seen with other targetable genomic changes in oncogenes found in ALK, KRAS, EGFR, or NSCLC (18). Judging by the results of an independent analysis of 166 ROS rearranged NSCLCs, 3.0% showed a concurrent PIK3CA mutation, 1.8% a concurrent KRAS mutation, and 0.6% a concurrent EGFR activating mutation. Concurrent ALK fusion was not observed in any case (18). Five cases of NSLCL with coexistence of ROS1 and EGFR mutations have been reported in the literature. Among these, one patient was operated and treated with chemotherapy at an adjuvant setting two patients received gefitinib as a first-line treatment, and achieved a partial response to the treatment, although no explanation was found regarding PFS. There was no information provided about the other cases (19,20). In a review article on co-mutations of ROS1 and KRAS, results were correlated with a lack of response to crizotinib therapy (21).

Literature contains reports on only two cases of ALK/ROS1 coexistence. Zhu et al. reported on a Chinese male 47-year-old smoker patient with a postoperative pathologic diagnosis of T1aN0M0. In a follow-up after 7 months (to August 2017), recurrence wasn't observed (4). In another study, results of fluorescent in situ hybridization (FISH) analysis were reported in a 77-year-old nonsmoker female patient with locally advanced lung adenocarcinoma, which was consistent with an ALK rearranged and ROS1. This patient was treated with crizotinib for 3 months, but PFS was not reported (22). In a study by Song et al., an analysis of 732 lung adenocarcinoma patients revealed 32 patients (4.4 %) with a ROS1 rearrangement, and only one patient with coexisting ROS1/ALK fusion. A 56-year-old male patient with metastatic lung adenocarcinoma was treated with first-line cisplatin and pemetrexed (PFS=5 months), followed by docetaxel on the second-line (PFS=2 months). Crizotinib was initiated as a third-line treatment, and a good response was reported after 2 months. The patient used crizotinib until the last follow-up with a PFS >1 year (23).

In the case of the current study, PFS was applied as 5 months with carboplatin and paclitaxel chemotherapy, 2 months with pemetrexed and cisplatin treatment and 7 months with crizotinib treatment.

CONCLUSION

Upon our review of reported cases with EGFR/ALK, EGFR/ROS1 and ROS1/ALK co-mutations in the literature, PFS was found to be worse in patients with ALK/EGFR and ROS1/EGFR co-mutations than those with a single mutation. Patients with ALK/EGFR concomitant mutations had good response with the treatment of EGFR inhibitors. A partial response was seen to be achieved with gefitinib in patients with EGFR/ROS1 co-mutations. Patients with ROS1/ALK co-mutations have a shorter PFS than patients with a single mutation and treated with crizotinib. Targeted agents did not work in patients with KRASco-mutations, where as chemotherapy seem to be more beneficial in such cases. Co-mutations can often negatively affect treatment efficacy, and so which mutation-directed treatments should be applied to patients with co-mutations? Should we choose chemotherapy over targeted agents? These are the questions that need to be answered. Additionally, more studies are needed to clarify which patients with concurrent mutations may benefit from chemotherapy or related tki.

Informed Consent:

All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

Conflict of Interest:

The authors have no conflict of interest to declare.

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