Cancer Chemotherapy and Pharmacology (2019) 83:1195–1196
https://doi.org/10.1007/s00280-019-03810-9

LETTER TO THE EDITOR

Short-time use of crizotinib as neoadjuvant in ALK-positive non-small cell lung carcinoma can be a chance for resectability

Saadettin Kilickap[1] · Sevgen Onder[2] · Omer Dizdar[1] · Mustafa Erman[1] · Aysegul Uner[2]

Received: 13 February 2019 / Accepted: 8 March 2019 / Published online: 12 March 2019

Abstract
Because of the rapid response to crizotinib, patients with ALK-positive locally advanced disease may become resectable with the use of neoadjuvant crizotinib. A 41-year-old never-smoking man who presented with asthma attack was found to have a suspicious lesion on chest X-ray after. Pathological examination was consistent with ALK(+), the signet-ring cell adenocarcinoma. Surgery was not performed because of mediastinal invasion of the mass. After 4 weeks of crizotinib treatment, a major response was achieved and the tumor became completely cavitary. Short-term neoadjuvant therapy with crizotinib for 4 weeks might be a promising therapy in locally advanced ALK-positive NSCLC and might provide a chance for resectability.

Keywords Lung cancer · ALK positive · Crizotinib · Neoadjuvant therapy

Background

Crizotinib, which is an ALK kinase inhibitor, was found to be superior to chemotherapy in the first-line setting for advanced stage ALK(+) NSCLC in PROFILE 1014 trial [1, 2]. Furthermore, responses to crizotinib were rapidly achieved within 6 weeks compared to 12 weeks with chemotherapy [3]. To our knowledge, there is no publication about the benefit of neoadjuvant use of crizotinib in patients with ALK(+) lung cancer.

Case

A 41-year-old man who presented with asthma attack was found to have a suspicious lesion on chest X-ray. The computed tomography (CT) scan revealed a paramediastinal cavitary mass of 40 × 35 mm in the left upper lobe. No significant hilar or mediastinal lymph node was observed in both CT and FDG-PET. Pathological examination of a trans-thoracic biopsy was consistent with the signet-ring cell adenocarcinoma. Surgery was not planned due to clinical and radiological signs of mediastinal invasion in the patient with swallowing difficulty. Upon fluorescence in situ hybridization assay, tumor tissues were found to harbor an EML4-ALK fusion gene. Neoadjuvant treatment with crizotinib 2 × 250 mg per day was started, considering higher response rates with ALK inhibitors compared with standard platinum-based chemotherapy. After 4 weeks of treatment, a major response was achieved and the tumor became completely cavitary (Fig. 1). At the 6th week, left upper lobectomy with lymph node dissection was performed. The size of the tumor was 3 cm, but only small tumor cells in the area. Four left hilar lymph nodes were also involved with extracapsular invasion. Visceral pleura and mediastinal fat tissue were also involved. The patient received four cycles of cisplatin and pemetrexed as adjuvant chemotherapy and radiotherapy was administered to the mediastinum. The patient is alive at 44th months' follow-up without any signs of recurrence.

Discussion

Preoperative chemotherapy for NSCLC has been extensively used, but its role in management of locally advanced NSCLC remains controversial due to the low response rate and toxicity of chemotherapy. The objective response rate (ORR) with combined chemotherapy regimens is about 40% [4, 5]. In the targeted-therapy era, molecular classification of

✉ Saadettin Kilickap
skilickap@yahoo.com

[1] Department of Medical Oncology, Hacettepe University Institute of Cancer, Hamamonu, 06100 Ankara, Turkey

[2] Department of Pathology, Hacettepe University Faculty of Medicine, Ankara, Turkey

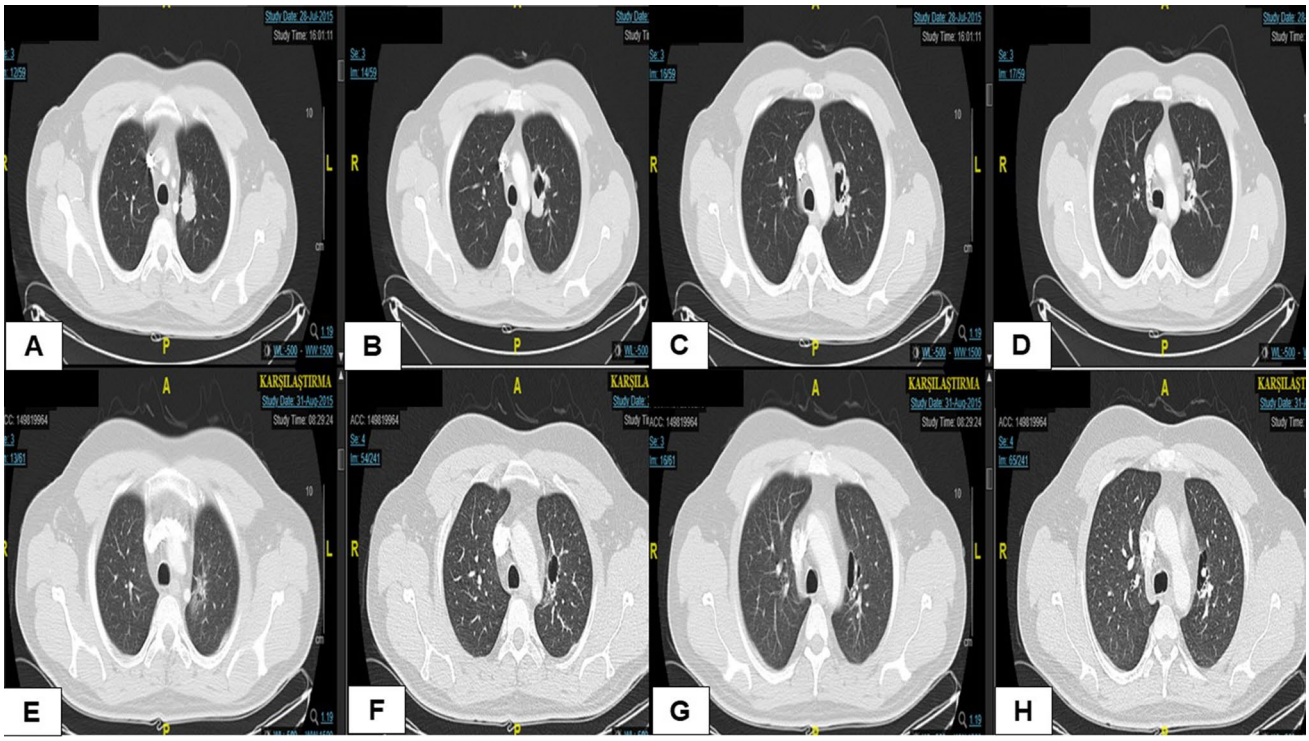

Fig. 1 Computed tomography imaging at the baseline (**a, b, c, d**) and after 4 weeks of crizotinib therapy (**e, f, g, h**)

primary tumor is very important because of higher response rates and lower toxicity with targeted therapies. Crizotinib was compared with combined chemotherapy regimen in the first-line setting in PROFILE 1014 trial [2]. Crizotinib improved ORR (74% vs 45%) and PFS (10.9 vs 7 months) compared with chemotherapy.

Response with ALK inhibitors can be more rapid than chemotherapy. Although response to standard chemotherapy occurs after 12 weeks, the time to response with ALK inhibitors varied from 3 to 8 weeks [3]. In our case, nearly complete remission was obtained after 4 weeks of crizotinib.

Currently, the role of ALK inhibitors in perioperative treatment of patients with ALK(+) NSCLC has not been established. To our knowledge, no previous data exist on the use of ALK inhibitors in neoadjuvant treatment of locally advanced stage NSCLC. Given the rapid tumor response achieved, a short-term neoadjuvant therapy with crizotinib for 4 weeks might be a promising therapy in locally advanced ALK(+) NSCLC and might provide a chance for resectability.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest No conflict of interest for all authors.

References

1. Solomon B, Varella-Garcia M, Camidge DR (2009) ALK gene rearrangements: a new therapeutic target in a molecularly defined subset of non-small cell lung cancer. J Thorac Oncol 4:1450–1454
2. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T et al (2014) First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 371:2167–2177
3. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ et al (2013) Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368:2385–2394
4. Scagliotti GV, Pastorino U, Vansteenkiste JF, Spaggiari L, Facciolo F, Orlowski FM et al (2012) Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. J Clin Oncol 30:172–178
5. Pless M, Stupp R, Ris HB, Stahel RA, Weder W, Thierstein S, SAKK Lung Cancer Project Group et al (2015) Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. Lancet 386:1049–1056