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ROS1-Rearranged Lung Cancer Successfully Resected after Response to Crizotinib: A Case Report

NAHOKO SHIMIZU[1], YUGO TANAKA[1,*]
MOTOKO TACHIHARA[2] and YOSHIMASA MANIWA[1]

[1]Department of Thoracic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan;
[2] Department of Respiratory Medicine, Kobe University Graduate School of Medicine, Kobe, Japan;
**Corresponding author*

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The usefulness of molecularly targeted therapy as a preoperative therapy for the c-ros oncogene 1 receptor tyrosine kinase (ROS1)-rearranged lung cancer has not been established. We present the case of ROS1- rearranged lung cancer successfully resected after response to crizotinib. The patient was a 71-year-old woman with prolonged cough. She was diagnosed with ROS1-rearranged lung adenocarcinoma (cT4N2M0, stage IIIB). After eight weeks of crizotinib treatment, right upper lobectomy with chest wall resection, angioplasty, and bronchoplasty were performed. The postoperative course was good, and the patient survived for 41 months after the surgery without recurrence. Surgical resection after molecularly targeted therapy for ROS1-positive lung cancer may lead to good local control.

INTRODUCTION

The c-ros oncogene 1 receptor tyrosine kinase (ROS1)-rearranged lung cancer is rare and comprises only 1% to 2% of non–small-cell lung cancers (NSCLC) (1,10). The ROS1 kinase domain has significant homology with the anaplastic lymphoma kinase (ALK) domain, and patients with ROS1-positive advanced non–-small-cell lung cancer share similar characteristics with patients with ALK-positive, such as adenocarcinoma histology, young age, and a high prevalence of nonsmoker status (7).

The ROS1-rearranged lung cancer has been reported to show good response to crizotinib, oral small-molecule tyrosine kinase inhibitor (TKI) of ALK, mesenchymal-epithelial transition (MET), and ROS1 kinases (6,9). In recent years, reports of salvage surgery for advanced non–small-cell lung cancer after response to EGFR-TKI have increased, and they suggest its potential safety and efficacy (3,4,12). However, there are no known investigations of preoperative crizotinib treatment in patients with NSCLC. We report the case of advanced ROS1-positive NSCLC in a patient who underwent salvage surgery after crizotinib treatment.

CLINICAL CASE

A 71-year-old woman was admitted to our hospital for a prolonged cough. Her medical history included dyslipidemia. Chest computed tomography (CT) showed a 91-mm tumor in the right upper lobe, with hilar and mediastinal lymphadenopathy (Fig. 1a, b). Tumor involvement of the third and fourth ribs was suspected, and the hilar lymph nodes extended to the right second carina. Positron emission tomography CT showed a strong fluorodeoxyglucose accumulation in the tumor (standardized uptake value max, 13.2) (Fig. 1c). Abnormal uptake was also found in one mediastinal lymph node (#4) and one hilar lymph node (#10) but not in any other area (Fig. 1d). A histopathological examination of a transbronchial lung biopsy specimen showed adenocarcinoma. ROS1 rearrangement was detected by reverse transcriptasepolymerase chain reaction. The patient was diagnosed with ROS1-rearranged lung adenocarcinoma (cT4N2M0, stage IIIB) and was treated with crizotinib (250 mg twice daily) as first-line chemotherapy. After 8 weeks of treatment, chest CT showed a significant decrease in the size of the tumor and lymph nodes (Fig. 1e, d), especially mediastinal lymph nodes were markedly reduced. Radiographic examination showed that the tumor was down staged to ycT3N1M0, stage IIIA; however, the patient experienced QT prolongation as a side-effect, making it necessary to discontinue administration of crizotinib.

With the down staging of the tumor to an operable state, salvage surgery was performed with a fourth intercostal posterolateral thoracotomy. Right-upper lobectomy was performed with the chest wall resection (parts of the third and fourth ribs), pulmonary arterioplasty (A2), bronchoplasty, systemic lymph node resection. Intraoperative findings showed rigid fibrosis surrounding the hilum of the upper lobe, considered to be a scar of a metastatic lymph node after crizotinib treatment. Direct tumor invasion of the third and fourth ribs was suspected,

Phone: +81 78 382 5750 Fax: +81 78 382 5751 E-mail: tanakay@med.kob-u.ac.jp

and resection was thought to require. A2 and the right second carina were sclerotic and required pulmonary arterioplasty and bronchoplasty. The operation took 7 h and 23 min, and the amount of blood loss was 450 mg.

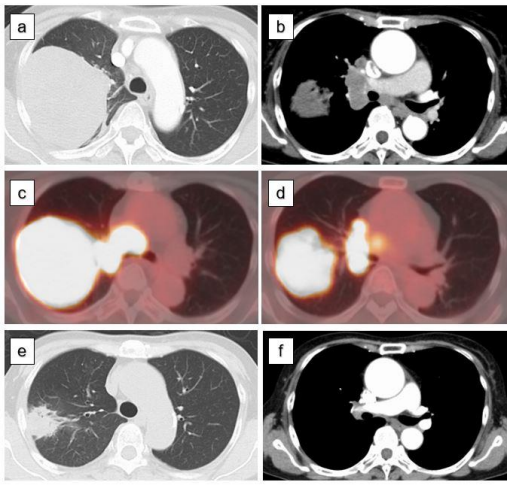

Figure 1.
Radiologic imaging of the chest.
a) Chest CT (pulmonary window).
A 91 × 90 × 76 -mm mass was identified at the right superior lobe and was suspected to have invaded the chest wall.
b) Chest CT (mediastinal window).
The enlarged hilar lymph nodes extended to the right second carina.
c, d) Positron emission tomography CT.
A strong fluorodeoxyglucose accumulation in the tumor, one mediastinal lymph node (#4), and one hilar lymph node (#10).
e, f) Chest CT of pulmonary window and mediastinal window. Chest CT performed after chemotherapy showed a marked reduction of the tumor and hilar and mediastinal lymph nodes.

The tumor was resected completely, and the postoperative course was good. The tumor measured 45mm × 33 mm, and a pathological evaluation revealed papillary adenocarcinoma. Tumor invasion into the intrathoracic fascia was suspected, but there were no viable tumor cells in the intrathoracic fascia and ribs. Lymph node metastasis was shown in the hilar lymph nodes, but not in the mediastinum lymph nodes, and tumor stage was yp-T3aN1M0, stage IIIA. Residual viable malignant cells were identified in less than one third of the cells within the tumor, and the resection margins were negative. Immunohistochemistry showed that the tumor was positive for ROS1 (Fig. 2 a, b). Adjuvant chemotherapy was not performed because it was determined that the tumor was under local control, and the patient survived for 41 months after surgery without tumor recurrence.

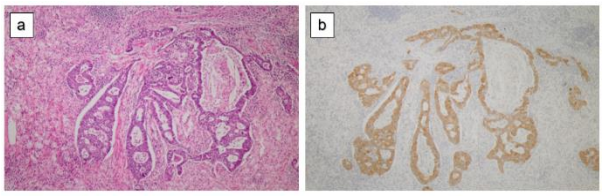

Figure 2.
Histological findings and immunohistochemical studies.
a) Hematoxylin-eosin staining of tissue shows papillary adenocarcinoma with strong atypia.
b) Immunostaining revealed that the carcinoma cells were positive for ROS1.

DISCUSSION

Many new drugs for lung cancer have been developed recently, including immune checkpoint inhibitors and molecular targeted drugs, and the treatment of advanced lung cancer has progressed markedly. In particular, treatment strategies for stage IIIA NSCLC are diverse and chosen individually through discussion among oncologists. Chemoradiotherapy is the standard treatment for unresectable stage III lung cancer (2,8) and was initially considered in our patient. However, radical irradiation was difficult because of the wide radiation range. Therefore, oral administration of crizotinib was started according to the treatment guidelines for stage IV NSCLC (9). Crizotinib produced rapid response; the size of the tumor and metastasis lymph node in the patient decreased significantly after the 8-week treatment, which is similar to results reported in previous studies (11). Crizotinib was discontinued because of the reduction in tumor size and the occurrence of QT prolongation side-effects, and we considered the transition to definitive chemoradiotherapy. However, after discussion among oncologists, we determined that the tumor could be resected because of the down staging, and a radical resection was performed.

It is unknown whether resection of a residual tumor after TKI treatment will lead to increased overall survival in patients with advanced NSCLC. Several researchers have reported that surgical treatment, which can be performed for local control and diagnostic intent after EGFR-TKI gefitinib administration, showed long-term survival in some patients (4, 5). However, the oncology background is quite different, depending on the report. The strategy of salvage surgery for super responders to targeted therapy warrants additional investigation. Hishida et al. reported that the mechanism of EGFR-TKIs is cytostatic rather than cytotoxic and that EGFR-TKIs could not eradicate micrometastatic tumor cells, even after a marked clinical response (4). Other studies have reported that the addition of local consolidative therapy, including radiation and surgery, after initial systemic therapy was feasible and led to good local control and significantly extended progression-free survival compared with maintenance treatment. In our patient, because the presence of ipsilateral mediastinal nodal metastases (N2) before

treatment with crizotinib was single station and local control by surgery was considered possible, salvage surgery seemed feasible.

Conversely, adjuvant therapy for patients who have undergone surgery after TKI is controversial. Many reports have shown continued use of TKIs postoperatively, but efficacy has not yet been proven. In our patient, we decided that local control was accomplished and did not perform postoperative therapy, but she has achieved long-term, recurrence-free survival without post-treatment.

The timing and validity of salvage surgery for residual lesions remain unclear when TKIs are prescribed to patients with advanced NSCLC with driver gene mutations. We report a case of salvage resection of ROS1-positive NSCLC after crizotinib treatment without complications. Additional clinical data are required to further investigate the role of surgery in patients with advanced NSCLC harboring ROS1 mutations.

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REFERENCES

1. **Bergethon, K., Shaw, A.T., Ou, S.I., Katayama, R., Lovly, C.M., McDonald, N.T., Massion, P.P., Siwak-Tapp, C., Gonzalez, A., Fang, R., Mark, E.J., Batten, J.M., Chen, H., Wilner, K.D., Kwak, E.L., Clark, J.W., Carbone, D.P., Ji, H., Engelman, J.A., Mino-Kenudson, M., Pao, W., and Iafrate, A.J.** 2012. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol **30:** 863-870.
2. Non-small Cell Lung Cancer Collaborative Group. 1995. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ **311:** 899-909.
3. **Hashimoto, K., Horinouchi, H., Ohtsuka, T., Kohno, M., Izumi, Y., Hayashi, Y., and Nomori, H.** 2012. Salvage surgery for a super-responder by gefitinib therapy for advanced lung cancer. Gen Thorac Cardiovasc Surg **60:** 851-854.
4. **Hishida, T., Nagai, K., Mitsudomi, T., Yokoi, K., Kondo, H., Horinouchi, H., Akiyama, H., Nagayasu, T., and Tsuboi, M.** 2010. Salvage surgery for advanced non-small cell lung cancer after response to gefitinib. J Thorac Cardiovasc Surg **140:** 69-71.
5. **Hishida, T., Yoshida, J., Aokage, K., Nagai, K., and Tsuboi, M.** 2016. Long-term outcome of surgical resection for residual or regrown advanced non-small cell lung carcinomas following EGFR-TKI treatment: report of four cases. Gen Thorac Cardiovasc Surg **64:** 429-433.
6. **Mazieres, J., Zalcman, G., Crino, L., Biondani, P., Barlesi, F., Filleron, T., Dingemans, A.M. Lena, H., Monnet, I., Rothschild, S.I., Cappuzzo, F., Besse, B., Thiberville, L., Rouviere, D., Dziadziuszko, R., Smit, E.F., Wolf, J., Spirig, C., Pecuchet, N., Leenders, F., Heuckmann, J.M., Diebold, J., Milia, J.D., Thomas, R.K., and Gautschi, O.** 2015. Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. J Clin Oncol **33:** 992-999.
7. **Pan, Y., Zhang, Y., Li, Y., Hu, H., Wang, L., Li, H., Wang, R., Ye, T., Luo, X., Zhang, Y., Li, B., Cai, D., Shen, L., Sun, Y., and Chen, H.** 2014. ALK, ROS1 and RET fusions in 1139 lung adenocarcinomas: a comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features. Lung cancer **84:** 121-126.
8. **Pritchard, R.S., and Anthony, S.P.** 1996. Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. A meta-analysis. Ann Intern Med **125:** 723-729.
9. **Shaw, A.T., Ou, S.H., Bang, Y.J., Camidge, D.R., Solomon, B.J., Salgia, R., Riely, G.J., Varella-Garcia, M., Shapiro, G.I., Costa, D.B., Doebele, R. C., Le, L.P., Zheng, Z., Tan, W., Stephenson, P., Shreeve, S. M., Tye, L.M., Christensen, J.G., Wilner, K.D., Clark, J.W., and Iafrate, A.J.** 2014. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Eng J Med **371:** 1963-1971.
10. **Takeuchi, K., Soda, M., Togashi, Y., Suzuki, R., Sakata, S., Hatano, S., Asaka, R., Hamanaka, W., Ninomiya, H., Uehara, H., Lim, Choi, Y., Satoh, Y., Okumura, S., Nakagawa, K., Mano, H., and Ishikawa, Y.** 2012. RET, ROS1 and ALK fusions in lung cancer. Nat Med **18:** 378-381.
11. **Wu, Y.L., Yang, J.C., Kim, D.W., Lu, S., Zhou, J., Seto, T., Yang, J.J., Yamamoto, N., Ahn, M.J., Takahashi, T., Yamanaka, T., Kemner, A., Roychowdhury, D., Paolini, J., Usari, T., Wilner, K.D., and Goto, K.** 2018. Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non-Small-Cell Lung Cancer. J Clin Oncol **36:** 1405-1411.
12. **Yamamoto, Y., Kodama, K., Maniwa, T., and Takeda, M.** 2017. Surgical resection of advanced non-small cell lung cancer after a response to EGFR-TKI: presentation of two cases and a literature review. J Cardiothorac Surg **12:** 98.