Editorial

The management of postoperative recurrence of non-small cell lung cancer harboring epidermal growth factor receptor (EGFR) mutation: what is the best way?

Hiroyuki Adachi[1], Yuichi Saito[2]

[1]Department of Thoracic Surgery, Kanagawa Cancer Center, Yokohama, Japan; [2]Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

Correspondence to: Hiroyuki Adachi, MD. Department of Thoracic Surgery, Kanagawa Cancer Center, Yokohama 241-8515, Japan.
Email: adachi-fam@white.plala.or.jp.

Comment on: Zheng Y, Zhou M, Arulananda S, *et al.* Management of non-small cell lung cancer with resistance to epidermal growth factor receptor tyrosine kinase inhibitor: case discussion. J Thorac Dis 2020;12:159-64.

Submitted Jan 21, 2022. Accepted for publication Mar 09, 2022.
doi: 10.21037/jtd-22-97
View this article at: https://dx.doi.org/10.21037/jtd-22-97

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have changed the strategy of treatment for advanced or postoperative recurrent non-small cell lung cancer (NSCLC). The first-generation TKI, gefitinib, appeared in 2002, and verified the relationship between EGFR mutation and its efficacy in 2004 (1). Several EGFR-TKIs have been developed and approved for the treatment of advanced/postoperative recurrent NSCLC worldwide to date, including gefitinib and erlotinib as first-generation TKIs, afatinib and dacomitinib as second-generation TKIs, and osimertinib as third-generation TKI. Compared to first-generation TKIs, second-generation TKIs as first-line therapy for advanced NSCLC with EGFR mutations improved patients' survival in clinical trials. In the LUX-Lung 7 trial, patients treated with afatinib showed longer progression-free survival (PFS) than those treated with gefitinib (2). In the ARCHER 1050 trial, patients treated with dacomitinib showed longer PFS and overall survival (OS) than those treated with gefitinib (3,4). According to these results, second-generation TKIs rather than first generation should be used as first-line therapy for patients with advanced NSCLC with EGFR mutation; however, it is often difficult in clinical practice to follow this principle because of their peculiar side effects (e.g., heavy diarrhea of afatinib and dermatitis acneiform of dacomitinib). Further, EGFR-TKIs eventually acquire resistance, even if they were effective for a while. According to Yu *et al.* (5), the mechanisms of acquired resistance are mainly T790M mutation (63%), followed by HER2 amplification (13%), MET amplification (5%), and small cell histologic transformation (3%). Osimertinib was developed as an irreversible EGFR-TKI that is selective for both EGFR and T790M resistance mutations, and first, it was shown to be superior to platinum-doublet in the treatment for patients with T790M-positive NSCLC in AURA3 trial (6). Thereafter, osimertinib was also shown to be superior to gefitinib in the treatment of patients with advanced NSCLC with EGFR mutation (Ex21L858R mutation or Ex19 deletion) in the FLAURA trial (7) and is now recognized as a drug for first-line molecular-targeted therapy for patients with advanced NSCLC with EGFR mutation. A summary of the prognostic benefit of second- and third-generation EGFR-TKIs over the first-generation TKIs is shown in *Table 1* (2-4,7,8).

Zheng *et al.* presented a patient who received first-line therapy with gefitinib for postoperative recurrence of NSCLC with pulmonary metastasis and single brain metastasis. However, disease progression occurred approximately 2 years after the administration of gefitinib, and anlotinib was administered without confirmation of the T790M mutation due to patients' refusal of biopsy, and consequently, the patient withdrew from the treatment due to side effects. In this case, we consider that osimertinib should be administered as a first-line therapy, if possible, as Dr. Arulananda and Dr. Um recommended in this article. Because the PFS benefit of osimertinib in patients with

Table 1 The summary of prognostic benefit of second- and third-generation EGFR-TKIs over the first-generation TKIs

	LUX-Lung 7 (2,8)	ARCHER 1050 (3,4)	FLAURA (7)
Study phase	IIb	III	III
Group	Afatinib *vs.* gefitinib	Dacomitinib *vs.* gefitinib	Osimertinib *vs.* gefitinib/erlotinib
Number of patients	160 *vs.* 159	227 *vs.* 225	279 *vs.* 277
ORR	70% *vs.* 56%; OR =1.87 (95% CI: 1.18–2.99); P=0.0083	75% *vs.* 70%; P=0.2224	80% *vs.* 76%; OR =1.27 (95% CI: 0.85–1.90); P=0.24
PFS	11.0 *vs.* 10.9 months; HR =0.73 (95% CI: 0.57–0.95); P=0.017	14.7 *vs.* 9.2 months; HR =0.59 (95% CI: 0.47–0.74); P<0.0001	18.9 *vs.* 10.2 months; HR =0.46 (95% CI: 0.37–0.57); P<0.001
OS	27.9 *vs.* 24.5 months; HR =0.86 (95% CI: 0.66–1.12); P=0.2580	34.1 *vs.* 26.8 months; HR =0.760 (95% CI: 0.582–0.993); P=0.0438	Not reached

EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; ORR, objective response rate; OR, odds ratio; CI, confidential interval; PFS, progression-free survival; HR, hazard ratio; OS, overall survival.

brain metastasis was reported in the FLAURA trial (7), and moreover, Colclough *et al.* (9) verified the higher blood-brain-barrier permeability of osimertinib than that of other TKIs in their *in vivo* and *in vitro* preclinical models, osimertinib might be preferred for this case.

As for the confirmation of the T790M mutation, it is essential to consider second-line therapy after developing resistance to EGFR-TKIs. Osimertinib becomes the ray of hope for patients if the mutation is detected, but it is useless if not detected. For patients whose metastatic nests are difficult to biopsy or who refuse invasive biopsies, such as transbronchial lung biopsy, liquid biopsy is a useful substitute. Takahama *et al.* (10) evaluated the efficacy of osimertinib in patients with T790M mutation-positive NSCLC detected by liquid biopsy. In their study, T790M mutation was detected in 74 of 276 patients, and the overall response rate in this population was 55.1% with the median DFS of 8.3 months. According to the preferable results, the authors should consider the use of liquid biopsy before administering anlotinib.

Although no detailed data about the lung metastatic lesions were reported in this article, we might consider surgical or radiotherapeutic intervention for single lung metastasis. Recently, some researchers advocated the concept of "oligo-recurrence" (11) and reported the efficacy of local therapy for such a limited recurrent status of postoperative NSCLC. Niibe *et al.* (12) reported that patients with NSCLC who received stereotactic radiotherapy for brain-only oligo-recurrence showed a favorable prognosis, and Hishida *et al.* (13) reported that initial definitive local therapy was associated with improved post-recurrence survival in patients with oligo-recurrence. Both were conducted among patients with oligo-recurrence restricted to a single organ; however, Sonoda *et al.* (14) reported in their study that among patients receiving radical local therapy, post-recurrence survival was particularly longer in patients with one or two recurrences that was not restricted to a single organ, and these patients were able to aim for post-recurrence cure. Although the efficacy of local therapy for postoperative recurrent NSCLC is not certain because the concept of "oligo-recurrence" appears recently and has non-uniform definition, it might be worth to consider applying local therapy (i.e., stereotactic radiotherapy for brain metastasis and partial resection for lung metastasis) for this case, if the lung metastasis was single.

In contrast, immune checkpoint inhibitor (ICI) therapy, another interesting therapeutic agent for advanced or postoperative recurrent NSCLC, as a second-line therapy for patients with NSCLC with EGFR mutation is somewhat disappointing. In their meta-analysis, Lee *et al.* (15) reviewed three studies that used ICI monotherapy as a second-line therapy for patients with NSCLC with EGFR mutation and had no positive impact on OS compared to docetaxel. Although studies have reported the efficacy of ICI + cytotoxic agent therapy compared with cytotoxic agents alone in a subset cohort of patients with previously treated advanced NSCLC with EGFR mutation (16,17), the administration of

chemotherapy with cytotoxic agents may be unavoidable in any case.

The management of postoperative recurrence of NSCLC harboring EGFR mutations is still uncertain, and the recommendations in NSCLC guidelines are drastically changed almost every year (18). Many strategies, including definitive local therapy, exist, and the treatment strategy for each patient must be considered through multidisciplinary discussions among the experts of lung cancer treatment.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-97/coif). HA serves as an unpaid editorial board member of the *Journal of Thoracic Disease*. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.
2. Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 2016;17:577-89.
3. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:1454-66.
4. Mok TS, Cheng Y, Zhou X, et al. Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib With Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. J Clin Oncol 2018;36:2244-50.
5. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 2013;19:2240-7.
6. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 2017;376:629-40.
7. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
8. Paz-Ares L, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol 2017;28:270-7.
9. Colclough N, Chen K, Johnström P, et al. Preclinical Comparison of the Blood-brain barrier Permeability of Osimertinib with Other EGFR TKIs. Clin Cancer Res 2021;27:189-201.
10. Takahama T, Azuma K, Shimokawa M, et al. Plasma screening for the T790M mutation of EGFR and phase 2 study of osimertinib efficacy in plasma T790M-positive non-small cell lung cancer: West Japan Oncology Group 8815L/LPS study. Cancer 2020;126:1940-8.
11. Niibe Y, Chang JY. Novel insights of oligometastases and oligo-recurrence and review of the literature. Pulm Med 2012;2012:261096.
12. Niibe Y, Nishimura T, Inoue T, et al. Oligo-recurrence predicts favorable prognosis of brain-only oligometastases in patients with non-small cell lung cancer treated with stereotactic radiosurgery or stereotactic radiotherapy: a multi-institutional study of 61 subjects. BMC Cancer 2016;16:659.
13. Hishida T, Yoshida J, Aokage K, et al. Postoperative oligo-

recurrence of non-small-cell lung cancer: clinical features and survival†. Eur J Cardiothorac Surg 2016;49:847-53.
14. Sonoda D, Matsuura Y, Kondo Y, et al. A Reasonable Definition of Oligo-Recurrence in Non-Small-Cell Lung Cancer. Clin Lung Cancer 2022;23:82-90.
15. Lee CK, Man J, Lord S, et al. Checkpoint Inhibitors in Metastatic EGFR-Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. J Thorac Oncol 2017;12:403-7.
16. Arrieta O, Barrón F, Ramírez-Tirado LA, et al. Efficacy and Safety of Pembrolizumab Plus Docetaxel vs Docetaxel Alone in Patients With Previously Treated Advanced Non-Small Cell Lung Cancer: The PROLUNG Phase 2 Randomized Clinical Trial. JAMA Oncol 2020;6:856-64.
17. Liu S, Wu F, Li X, et al. Patients With Short PFS to EGFR-TKIs Predicted Better Response to Subsequent Anti-PD-1/PD-L1 Based Immunotherapy in EGFR Common Mutation NSCLC. Front Oncol 2021;11:639947.
18. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Small Cell Lung Cancer Version 1.2022. Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Cite this article as: Adachi H, Saito Y. The management of postoperative recurrence of non-small cell lung cancer harboring epidermal growth factor receptor (EGFR) mutation: what is the best way? J Thorac Dis 2022;14(4):812-815. doi: 10.21037/jtd-22-97