

Adjuvant targeted therapy for resected NSCLC: to be or not to be?

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Lung cancer, one of the most frequent malignant tumors in the world, is the main cause of cancer-related death nowadays (1). Radical surgery remains the cornerstone of treatment for early-stage non-small cell lung cancer (NSCLC). However, despite undergoing potentially curative surgery, patients with stage I, II, or IIIa NSCLC are at substantial risk for recurrence and death (2). Five-year survival estimates range from between 50% and 70% for patients with stage I disease to between 10% and 30% for patients with stage IIIa disease (3). Because treatment failure following potential curative surgery is frequently encountered, adjuvant systemic therapy has become a rational approach to reduce the risk for recurrence and improve overall survival (OS) outcomes (4). To confirm the survival benefit resulting from adjuvant chemotherapy, the large meta-analysis (LACE) which included individual patients from five large adjuvant trials enrolled 4,584 patients with completely resected NSCLC and showed that platinum-based adjuvant chemotherapy was associated with a 3.9% and 5.4% lower risk for death at 3 and 5 years than with surgery alone (HR for death, 0.89; 95% CI, 0.82–0.96; P=0.005). Especially, the survival benefit was statistically significant for patients with stage II and IIIa disease (HR, 0.83), while the survival benefit did not reach statistical significance (HR, 0.93) for patients with stage IB (5). Based on these available data, guidelines from Cancer Care Ontario and the American Society of Clinical Oncology recommended platinum-based adjuvant chemotherapy for patients with completely resected stage II or IIIa NSCLC (6). Moreover, in 2010, the NSCLC

Meta-analyses Collaborative Group reported on a meta-analysis of 34 clinical trials including 8,447 patients, which addressed the benefit of adjuvant chemotherapy for resected NSCLC. Their results showed that cisplatin-based adjuvant chemotherapy could improve in 5-year survival of 5% for both stage II (from 40% to 45%) and stage III (from 30% to 35%) diseases (7).

Four cisplatin-based chemotherapy regimens for adjuvant treatment including vinorelbine, paclitaxel, gemcitabine and pemetrexed are clinically applied. Pemetrexed is recommended for non-squamous carcinoma, while the others are usually used for both adenocarcinoma and squamous cell carcinoma. However, the benefit of adjuvant chemotherapy is not without cost, and some patients experience severe toxicity. In the LACE meta-analysis, there was a 66% incidence of grade 3 or 4 adverse events. A significant interaction was seen between the chemotherapy and the World Health Organization performance status (PS). A better PS was associated with a significantly increased chemotherapy effect, while a worse PS meant more adverse effects (5). Accordingly, not all the patients have a survival benefit from adjuvant chemotherapy. And more questions remain addressing this issue.

EGFR tyrosine kinase inhibitors have been confirmed as the first-line treatment for EGFR-mutant advanced NSCLC. Several trials have shown superior progression-free survival (PFS) and fewer side effects compared with doublet chemotherapy (8-10). Naturally, some researchers pay more attention on the effect of EGFR-TKIs for resected NSCLC as adjuvant therapy. There are four prospective clinical

trials (BR19, RADIANT, SELECT and ADJUVANT/CTONG1104) evaluating the effect of EGFR-TKIs as adjuvant treatment for EGFR mutant early-stage NSCLC. In BR19 study, they evaluated gefitinib as adjuvant therapy for unselected patients with inoperable stage III NSCLC and completely resected patients with stage IB–IIIA NSCLC. And their results showed administration of gefitinib as adjuvant therapy could not provide improved disease-free survival (DFS) or overall survival. Noticeable, researchers in the study did not assess the EGFR mutation status for patients before treatment (11). In RADIANT study, 973 patients with resected IB to IIIA NSCLC were randomly assigned to erlotinib group taking erlotinib 150 mg once per day or placebo for 2 years. Researchers evaluated EGFR protein expression by immunohistochemistry or EGFR amplification by FISH for all patients. And EGFR mutant status was confirmed in only 16.5% patients in this study. Their results showed that adjuvant erlotinib did not prolong DFS in patients with EGFR protein expressing NSCLC or in EGFR mutant subgroup (12). In SELECT study, which was a first study testing the efficacy of adjuvant erlotinib in EGFR-mutant NSCLC, 100 patients with resected stage IA–IIIA NSCLCs harboring TKI-sensitizing EGFR mutation received erlotinib 150 mg/day for 2 years after completion of standard adjuvant chemotherapy and/or radiotherapy. In the study, the 2-year DFS was 90%. Median DFS and OS had not been reached. And they concluded sensitive patients had an improved 2-year DFS treated with adjuvant erlotinib compared to historical genotype-matched controls. This study was a phase II and single armed trial (13). Accordingly, the value of EGFR-TKI as adjuvant treatment for resected NSCLC is still unclear. The ADJUVANT/CTONG1104 study is a well-designed, first phase III randomized clinical trial to assess the efficacy of Gefitinib compared with cisplatin-based chemotherapy in patients with sensitive EGFR mutation receiving completed resection for stage II–IIIA NSCLC. Compared with the above three trials, this trial has the more specific object of study and stricter criteria of patient enrollment. Especially, this trial only focused on EGFR mutant patients, who were the real targets to EGFR-TKI treatment. Greatly, results of this trial showed that treatment with gefitinib was associated with significantly longer DFS than was vinorelbine plus cisplatin in patients with completely resected, stage II–IIIA, EGFR mutant patients with NSCLC. Patients received gefitinib treatment had the DFS benefit of about 10 months compared with those received vinorelbine plus cisplatin

treatment (28.7 *vs.* 18.0 months, median DFS). In addition, these patients experienced fewer adverse events (58% *vs.* 80%) and even serious events (7% *vs.* 23%) compared with those received chemotherapy (14). The ADJUVANT/CTONG1104 study is very important for adjuvant EGFR-TKI as a potential treatment for resected stage II–IIIA NSCLC. On the other hand, in my point view, the overall survival is much more important than DFS for patients after surgery. Unluckily, this trial did not show us the mature data for overall survival. It is very possible that the OS between the two groups of patients in this study will be similar considering the effect of treatment crossover in the future. Patients received gefitinib will get chemotherapy because of EGFR-TKI tolerance, and vice versa. Therefore, the DFS benefit could not be converted to OS benefit. In addition, tolerance of EGFR-TKI is a big issue. In a sense, it will appear earlier if patients received the tablets earlier. Moreover, the appropriate duration of adjuvant EGFR-TKI treatment is still uncertain. Why did researchers administer gefitinib for two years? Had all the patients experience drug tolerance after two years in this study? It would be better if the authors give us more information. Furthermore, I notice that six patients with pathologic squamous cell carcinoma had EGFR mutation in this study. As far as I know, there is no EGFR mutation in squamous cell lung cancer. I have no idea why patients with squamous cell carcinoma had EGFR sensitive mutation in this trial.

In conclusion, further investigations are needed to classify the role of adjuvant EGFR-TKI treatment for resected early-stage NSCLC. Especially, it is interesting whether adjuvant EGFR-TKI treatment could provide the benefit of overall survival compared with the traditional chemotherapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11-30.
2. Ponn RB, Lo Cicero J III, Daly BDT. Surgical treatment

- of non-small cell lung cancer. In: Shields TW, Lo Cicero J III, Ponn RB, et al., editors. *General Thoracic Surgery* (ed6). Philadelphia, PA: Lippincott Williams & Wilkins, 2005:1548-87.
3. Gloeckler Ries LA, Reichman ME, Lewis DR, et al. Cancer survival and incidence from the Surveillance, Epidemiology, and End Results (SEER) program. *Oncologist* 2003;8:541-52.
 4. Bordoni R. Consensus conference: multimodality management of early- and intermediate-stage non-small cell lung cancer. *Oncologist* 2008;13:945-53.
 5. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008;26:3552-9.
 6. Pisters KM, Evans WK, Azzoli CG, et al. Cancer Care Ontario and American Society of Clinical Oncology Adjuvant Chemotherapy and Adjuvant Radiation Therapy for Stages I-III A Resectable Non-Small-Cell Lung Cancer Guideline. *J Clin Oncol* 2007;25:5506-18.
 7. NSCLC Meta-analyses Collaborative Group, Arriagada R, Auperin A, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet* 2010;375:1267-77.
 8. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomized phase 3 trial. *Lancet Oncol* 2010;11:121-8.
 9. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label randomized phase 3 study. *Lancet Oncol* 2011;12:735-42.
 10. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-57.
 11. Goss GD, O'Callaghan C, Lorimer I, et al. Gefitinib versus placebo in completely resected non-small-cell lung cancer: results of the NCIC CTG BR19 study. *J Clin Oncol* 2013;31:3320-6.
 12. Kelly K, Altorki NK, Eberhardt WE, et al. Adjuvant erlotinib versus placebo in patients with stage IB-III A non-small-cell lung cancer (RADIANT): a randomized, double-blind, phase III trial. *J Clin Oncol* 2015;33:4007-14.
 13. Pennell NA, Neal JW, Chaft JE, et al. SELECT: a multicenter phase II trial of adjuvant erlotinib in resected early-stage EGFR mutation-positive NSCLC. *Proc Am Soc Clin Oncol* 2014;32:abstr 7514.
 14. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-III A (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. *Lancet Oncol* 2018;19:139-48.

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