

## Re-challenge treatment of small-molecular inhibitors in NSCLC patients beyond progression

Lingli Tu<sup>1</sup>, Lan Sun<sup>1,2</sup>

<sup>1</sup>Division of Thoracic Cancer, Cancer Center, West China Hospital, West China School of Clinical Medicine, Sichuan University, Chengdu, China; <sup>2</sup>Department of Oncology, People's Hospital of Bishan County, Chongqing, China

*J Thorac Dis* 2012;4(6):647-649. DOI: 10.3978/j.issn.2072-1439.2012.10.14

In the past ten years, small-molecular inhibitors have presented exclusive promise on non-small cell lung cancer (NSCLC) and long-term survival has been achieved (1,2). However, drug resistance is still a huge blockade for clinical practice. Some recent studies greatly encouraged clinical physicians due to favorable outcomes obtained in NSCLC patients with disease progression (PD) after re-challenge treatment of small-molecular inhibitors such as crizotinib, gefitinib and erlotinib (3,4). It provided important evidences to guide the standard of personal treatment. However, there is still a long way to go.

The re-challenge treatment beyond PD has two available strategy scenarios. The first one is continuation of inhibitor including dose increments. Generally, treatment should be terminated when PD is confirmed. However, some evidences confirmed that it's still able to achieve long-term survival after continuation of inhibitors. In a prospective study by Camidge *et al.*, it suggested the implication of continuous using crizotinib beyond PD in ALK-positive non-small-cell lung cancer (3). It showed that 30.8% (12/39) of patients continued to use crizotinib for  $\geq 6$  months from the time of their initial investigator defined PD. We noted that in those patients, sites of initial progression were composed of 5 in brain metastases (n=10), 4 in target lesion (n=21), 2 in solo lesion (adrenal gland or lung nodules) and 1 in clinical progression. Moreover, there were 3 patients in group with initial status of stable disease (SD, n=10) and 9 with partial response (PR, n=27). It revealed that 30%-33.3% of ALK-positive patients with SD/PR would benefit from continuation of crizotinib beyond PD. The best site benefited from crizotinib treatment in those patients was brain metastases

(50%, 5/10). Authors suggest those patients potentially amenable to local treatment. The main reasons of acquired resistance were primary pharmacokinetic failure in brain, classical mechanisms of resistance and sole-clone evolution. However, some issues should be addressed. Due to the limited tissue, ROS arrangement, MET amplification and other popular factors such as G1269A mutation were not examined, which may impact on the effect of ALK inhibitor (5,6). Moreover, it's not clear whether other approaches were added to those patients concurrently.

Anecdotally, continuous using gefitinib also contributed to long-term survival. In a retrospective study by Nishie *et al.*, 64 patients with gefitinib-sensitizing EGFR mutations were enrolled (4). Among them, 39 patients were included in the group of continuing EGFR-TKI beyond PD; 25 patients were switched to the other group of chemotherapy alone. The median Overall Survival (OS) were 32.2 versus 23.0 months, presenting a significant difference between them ( $P=0.005$ ). Cox analysis confirmed it's an independent prognostic factor in those patients with activating mutations. Authors implied that continuation of EGFR-TKI would be beneficial in reducing risks of adverse effects caused by chemotherapy and reasonable for suppression of EGFR-TKI sensitive clones. However, it should be cautious due to the limited number of patients.

The second scenario of re-challenge treatment is re-starting of inhibitor beyond PD with add-on approaches including chemotherapy, radiotherapy and other inhibitors concurrently/sequentially. Generally, it's not rare. Recently, a retrospective study by Namba *et al.* (ESMO 2012, Abstract 1253p) showed a similar result that gefitinib re-starting treatment beyond PD could prolong OS in advanced NSCLC patients ( $P<0.001$ ), and it's well tolerable even for long-term administration. Some regimens involved in patients' history. A patient with the longest survival time of 3,867 days even received 11 regimens. In addition, it's reported that a 35-year-old patient with PD had an effective effect after reintroduction of gefitinib (7). Moreover, there were 3 cases with continuation of erlotinib in combination with pemetrexed after PD. Of these, 2 had duration time post add-on treatment beyond more than 3 months (7). Thus, adding

Corresponding to: Lan Sun. Department of Oncology, People's Hospital of Bishan County, Bishan, Chongqing 402760, China. Email: sunlan6203@163.com.

Submitted Oct 18, 2012. Accepted for publication Oct 24, 2012.  
Available at [www.jthoracdis.com](http://www.jthoracdis.com)

ISSN: 2072-1439

© Pioneer Bioscience Publishing Company. All rights reserved.

drugs on TKI would be a promising option to those patients (8).

In the past, re-challenge treatment of chemotherapy was often unsuccessful. Thus, the main questions are addressed: What is the main mechanism of inhibitor re-challenge treatment? How to identify the optimal treatment strategy beyond PD? Until now, the mechanism is unknown. More and more evidences present that it may be favorable to acquired resistance of inhibitors but not to de novo resistance. Thus, acquired resistance is the first thing needed to be clearly defined. Jackman *et al.* proposed 4 criteria for it (9). However, it's still controversial (10). Activating mutations examination is imperfect, because a proportion of patients with TKI-sensitizing mutation has de novo resistance and fails to treatment. Those patients with initial status of PD should be excluded. Also, for exclusion of patients with acquired resistance to gefitinib, 50% PD patients have T790M mutation (11) and 22% have MET amplification (12). The rest of them remain unclear. Moreover, even if T790M exists but combines with activating mutations, the patients could still achieve favorable outcome (10). In the case of failure of gefitinib, continuous using erlotinib would have achieved 10% of tumor response rate (13). It's also documented that chemotherapy, second-generation inhibitors and monoclonal antibodies could overcome acquired resistance of inhibitors (14). In fact, patients with inhibitor re-challenge treatment are frequently combined with radiation treatment and might benefit from local control. Taken together, we believe that other approaches should assist inhibitor re-challenge. A variety of treatment regimens exist in a patient's history, and we have yet to uncover the interrelationships of them all. Future studies should aim to warrant the sequence of main approaches concurrently, sequentially or solely. Therefore, dynamic treatment regimen analysis (DTRA) may promise to achieve this. On the other hand, we speculate internal factors should contribute to this action, such as ROS rearrangement, MET amplification, T790M mutation, G1269A and so on. Other external mechanisms such as microenvironment may be involved as well (15,16). The existence of these popular factors and their possible mechanisms should be elucidated. Additionally, cell transformation from NSCLC to SCLC was documented (17). It may be a new mechanism of drug resistance. Thus, re-biopsy should be recommended.

The indication of inhibitor re-challenge is still unclear. We suggest that NSCLC patients initially responded to small-molecular inhibitors (CR, PR and SD) should be recommended to receive inhibitors re-challenge treatment. Please note that the meaning of responder is not equal to status of activating mutation. The proportion of benefit is approximate 10-30%, maximum 50%. PR and SD patients may have equal probability. CR patients are under investigation. Those patients with sites of brain metastases may be the best candidates. Patients with PD sites of target lesion may have unfavorable outcomes. However, dose increments or other add-on approaches may be alternative to overcome it.

Additionally, we suggest patients in old age or poor Performance Status (PS) scores should have higher priority (3,4).

In conclusion, to date, many studies have shown that small-molecular inhibitors promise to contribute a long-term survival. It is possible that other add-on approaches and unknown external/internal factors may impact it. Gaining a detailed understanding of the mechanism will possibly help physicians to manipulate the personal treatment strategy. Thus, more attentions should be paid to re-challenge treatment of small-molecular inhibitors after PD. It deserves further investigations.

## Acknowledgements

*Disclosure:* The authors declare no conflict of interest.

## References

1. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-57.
2. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncol* 2011;12:1004-12.
3. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol* 2012;13:1011-9.
4. Nishie K, Kawaguchi T, Tamiya A, et al. Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Beyond Progressive Disease: A Retrospective Analysis for Japanese Patients with Activating EGFR Mutations. *J Thorac Oncol* 2012;7:1722-7.
5. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol* 2012;30:863-70.
6. Doebele RC, Pilling AB, Aisner DL, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin Cancer Res* 2012;18:1472-82.
7. Kim YH, Fukuhara A, Mishima M. Should Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Be Continued beyond Progressive Disease? *Case Rep Oncol* 2011;4:470-4.
8. Jänne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. *J Clin Oncol* 2012;30:2063-9.
9. Jackman D, Pao W, Riely GJ, et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *J Clin Oncol* 2010;28:357-60.
10. Mok TS. Living with imperfection. *J Clin Oncol* 2010;28:191-2.
11. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2005;352:786-92.
12. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007;316:1039-43.
13. Cho BC, Im CK, Park MS, et al. Phase II study of erlotinib in advanced

- non-small-cell lung cancer after failure of gefitinib. *J Clin Oncol* 2007;25:2528-33.
14. Lovly CM, Horn L. Strategies for Overcoming EGFR Resistance in the Treatment of Advanced-Stage NSCLC. *Curr Treat Options Oncol* 2012;13:516-26.
  15. Yao Z, Fenoglio S, Gao DC, et al. TGF-beta IL-6 axis mediates selective and adaptive mechanisms of resistance to molecular targeted therapy in lung cancer. *Proc Natl Acad Sci U S A* 2010;107:15535-40.
  16. Suda K, Tomizawa K, Fujii M, et al. Epithelial to mesenchymal transition in an epidermal growth factor receptor-mutant lung cancer cell line with acquired resistance to erlotinib. *J Thorac Oncol* 2011;6:1152-61.
  17. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011;3:75ra26.



**Cite this article as:** Tu L, Sun L. Re-challenge treatment of small-molecular inhibitors in NSCLC patients beyond progression. *J Thorac Dis* 2012;4(6):647-649. DOI: 10.3978/j.issn.2072-1439.2012.10.14