Perspective

# Tyrosine kinase inhibitors re-treatment beyond progression: choice and challenge

**Ru Zhang[1], Lingli Tu[2], Lan Sun[2]**

[1]Department of Gerontology, Chengdu Military General Hospital, Chengdu 610083, China; [2]Department of Oncology, the People's Hospital of Bishan County, Bishan, Chongqing 402760, China

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

**Abstract:** Tyrosine kinase inhibitors (TKIs) are highly effective agents for the treatment of lung cancer which harbors activated gene mutation. However, for patients with failure of TKI, TKI re-treatment beyond progression (TRBP) is still a potential option that has been proven by many literatures. In this review, we summarize the clinical evidence of TRBP and discuss the potential mechanisms to overcome TKI-acquired resistance

**Keywords:** Non-small cell lung cancer (NSCLC); tyrosine kinase inhibitor (TKI); re-treatment; EGFR; acquired resistance

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In the past decade, tyrosine kinase inhibitors (TKIs) including gefitinib and erlotinib have been proven effective in the treatment of patients with non-small cell lung cancer (NSCLC) (1,2). Moreover, it's reported that TKI re-treatment beyond progression (TRBP) also contributes to achieve a long-term survival (3,4). However, who should receive TRBP? This issue is still unclear.

## Predictors

Generally, the best evidence for TRBP predictors should be derived from large-scale randomized control trails or high-level Meta-analysis. Unfortunately, it's lack now. Two on-going studies including ASPIRATION and IMPRESS may address this issue soon. Recently *EGFR* gene mutation is recognized as the best predictor of TKI response. Some studies suggest it a potential predictor of TRBP for NSCLC patients (4). However, as we know, *EGFR* gene tests are only launched in very few hospitals of China. A large number of patients can not do such tests in primary hospitals without test equipment. Thus, those patients have to be switched to chemotherapy without opportunity to receive TRBP. Moreover, regardless of re-biopsy risk, expensive cost of health care is another question. A convenient and effective predictor is required urgently. In fact, gene tests are not irreplaceable. Even for EGFR mutation test, the best predictor to TKI response, the predictive accuracy is 70% approximately. It may be taken place by the other approaches such as clinically identified models.

In the previous reports (5-7), TRBP has been proven effective for TKI responders. A Japanese report showed that a 39-year-old male patient received initial crizotinib treatment and achieved a significant response persisted for 4 months, after disease progression, crizotinib was discontinued. However, five months after that, crizotinib was re-administrated and still achieved a significant response persisted for 2.5 months (8). Another study also suggests that TKI re-treatment is better option after failure of TKI treatment for NSCLC patients once responded from the prior TKI treatment (9). Taken together, initial response to TKI may be a potential predictor of TRBP. Based on these promising findings, a series of clinically TKI-failure models were established and explored using Bayesian discriminant analysis, named as dramatic progression group, gradual progression group and local progression group. It is a novel method derived from clinical experiences and mathematical calculation. Novel criteria for TKI failure models in NSCLC were addressed (10). Conclusively, TRBP should

be given in those with slow disease progression or less new lesions rather in those with massive disease progression. It's meaningful in the developing countries.

## Mechanisms

TKI-acquired resistance has many sorts of mechanisms. The main mechanisms are summarized as follows (11): (I) EGFR signaling pathway is abnormal such as EGFR amplification, T790M mutation and other components disorders; (II) regardless of whether EGFR signaling pathway is normal or abnormal, the other signaling bypasses take its place, such as c-MET amplification and PIK3CA mutation; (III) histopathological features have been changed, such as small cell lung cancer (SCLC) transformation and epithelial to mesenchymal transition (EMT). To overcome these, the relative therapies are various. EGFR-TKI re-treatment is one of them that may be due to the complicated molecular reactions. Until now, it is unclear. To our knowledge, we speculate that despite of disease progression, EGFR signaling crosstalk remains stationary so that it plays a role on cancer cell potentially. The EGFR pathway factors could be re-activated by TKI re-treatment or other regimens. Thus, TKI re-treatment with or without time interval could be still at work. However, for patients with EGFR pathway dysfunction, such as rapid progression with SCLC transformation, TKI re-treatment might be out of work.

## Hypothesis

Until now, TKI-retreatment is an extremely controversial topic. Who and when should receive TKI-retreatment after failure of TKI? Although it is unclear, we proposed our hypothesis as follows: three time-points are supposed in a TKI-using patient's history including time-point before initial TKI treatment (named as "A"), time-point after initial TKI treatment but before TRBP (named as "B"), and time-point after TRBP (named as "C"). In our hypothesis, two groups ("a" and "b") are defined as a set of potential predictors in their corresponding time-points ("A" and "B"), including initial responses, gene tests by biopsy/re-biopsy, best change of baseline, biomarker expression and other criteria.

Generally, a time interval is shorter, a prediction is more accurate; however, applicable value of prediction should be decreased due to a narrow time window. Thus, EGFR mutation has been proven to be the best predictor in group "a" for prediction of TKI initial response (B), but may be not the best in group "b" for TRBP (C). Some clinical feathers such as initial response in group "b" should be better in terms of inexpensive cost and available definition for TRBP indications. In the previous report, three mainly clinical parameters as duration of disease control (DDC), the volume doubling time (VDT) of target lesions and scores for progression in non-target lesions. Additionally, scores for clinical symptom were analyzed as well (10). In another report in ESMO 2012 (Abstract 1253p), NSCLC patients initially responded to TKI (CR, PR and SD) should be suitable to receive TRBP. The benefit rate (SD and PR) is approximate 30-33% (5). Therefore, initial response which defined as best TKI response lasting for four weeks represents time duration to TKI response before VDT in time-axis. It is an important parameter so that should be analyzed. However, clinical symptoms which represents patient's basic diseases and performance status (PS) are complicated and non-specific. In previous reports, patients with old age or poor PS scores have been advised to receive TRBP (3,4). Thus, it should be recommended as a candidate parameter with a considerable weight.

## Conclusions

Definitely, TRBP based on some intrinsic properties deserves further investigations. To date, more and more studies focused on clinical parameters rather than molecular features for prediction of TKI treatment such as first cycle rash (12). Herein, clinical features such as initial response may imply a good response to TRBP. It will be approved by two prospective studies (IMPRESS and ASPIRATION), and able to select the candidates for TRBP efficiently and inexpensively.

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## 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. Tu L, Sun L. Re-challenge treatment of small-molecular inhibitors in NSCLC patients beyond progression. J Thorac Dis 2012;4:647-9.
6. 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.
7. Watanabe S, Tanaka J, Ota T, et al. Clinical responses to EGFR-tyrosine kinase inhibitor retreatment in non-small cell lung cancer patients who benefited from prior effective gefitinib therapy: a retrospective analysis. BMC Cancer 2011;11:1.
8. Matsuoka H, Kurata T, Okamoto I, et al. Clinical response to crizotinib retreatment after acquisition of drug resistance. J Clin Oncol 2013;31:e322-3.
9. Song Z, Yu X, He C, et al. Re-administration after the failure of gefitinib or erlotinib in patients with advanced non-small cell lung cancer. J Thorac Dis 2013;5:400-5.
10. Yang JJ, Chen HJ, Yan HH, et al. Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer. Lung Cancer 2013;79:33-9.
11. 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.
12. Lee SM, Khan I, Upadhyay S, et al. First-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy (TOPICAL): a double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2012;13:1161-70.

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