The Epidermal Growth Factor Receptor D761Y Mutation and Effect of Tyrosine Kinase Inhibitor

Shinichi Toyooka, Hiroshi Date, Akiko Uchida, et al.

Clin Cancer Res 2007;13:3431.

The Epidermal Growth Factor Receptor D761Y Mutation and Effect of Tyrosine Kinase Inhibitor

To the Editor: We read with great interest the November 1, 2006 article by Balak et al. (1) reporting that the epidermal growth factor receptor (*EGFR*) D761Y mutation was a "novel secondary mutation" that appeared in a metastatic brain lesion after the acquisition of gefitinib resistance. The authors examined biological properties of D761Y and found a slight (<10-fold) decrease in the tyrosine-phosphorylated protein by gefitinib, compared with that in a L858R, using transient transfections to 293T cells (1). In addition, they established stable transfectants with D761Y plus L858R and found that this transfectant was 2-fold less sensitive to growth inhibition by gefitinib than L858R alone. We would like to address two issues concerning the results presented by Balak et al. (1).

First, we also reported the same type of mutation (*EGFR* D761Y plus L858R) in a resected tumor that had not received prior therapy (2). This patient did not respond to gefitinib; the same mutation was detected in a metastatic liver lesion with a dominant mutant allele. Unfortunately, Balak et al. were unable to evaluate the D761Y mutation in the pretreatment specimen because of no remaining DNA; thus, it was unclear whether the D761Y mutation was "inherent" or "secondary" to gefitinib treatment. However, our case indicates the presence of an "inherent" D761Y mutation in a non–small-cell lung cancer. Second, we also introduced D761Y plus L858R or T790M plus L858R expression vectors to 293T cells transiently to examine whether EGFR phosphorylation was affected by gefitinib (at concentrations of 0, 0.2, and 2 μmol/L). Whereas the phosphorylation of the T790M plus L858R transfectant was, as expected, not inhibited by gefitinib at least at a concentration of 2 μmol/L (3), that of the D761Y plus L858R transfectant was clearly inhibited at a concentration of 0.2 μmol/L, a concentration that is regarded to indicate "sensitivity" to gefitinib *in vitro* (4, 5). These findings suggested that the D761Y plus L858R mutant may be a little less sensitive than the L858R mutant, but this mutant effect *in vitro* was not enough to explain the resistance to gefitinib shown in the clinical case, suggesting that other factors may cause the resistance. Of interest, the D761Y plus L858R mutant may be biologically aggressive, as preliminary data suggested a "gain-of-function" property of the D761Y mutant (1).

Resistance to tyrosine kinase inhibitor (TKI) is a critical issue that must be overcome. Further investigation for rare mutations may yield clues for novel strategies to overcome inherent and acquired resistance to TKI.

Shinichi Toyooka
Hiroshi Date
Departments of Cancer and Thoracic Surgery, Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Okayama, Japan

Akiko Uchida
Katsuyuki Kiura
Hematology, Oncology, and Respiratory Medicine, Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Okayama, Japan

Minoru Takata
Department of Human Genetics, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan

References

1. Balak MN, Gong Y, Riely GJ, et al. Novel D761Y and common secondary T790M mutations in epidermal growth factor receptor-mutant lung adenocarcinomas with acquired resistance to kinase inhibitors. Clin Cancer Res 2006;12:6494–501.
2. Tokumo M, Toyooka S, Ichihara S, et al. Double mutation and gene copy number of EGFR in gefitinib refractory non-small-cell lung cancer. Lung Cancer 2006;53:117–21.
3. 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.
4. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129–39.
5. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497–500.

doi:10.1158/1078-0432.CCR-07-0070