EGFR delE709_T710insD

A Rare but Potentially EGFR Inhibitor Responsive Mutation in Non–Small-Cell Lung Cancer

Allison Ackerman, MD, Michael A. Goldstein, MD, Susumu Kobayashi, MD, PhD, and Daniel B. Costa, MD, PhD

Among the various somatic mutations in the epidermal growth factor receptor (*EGFR*) found in non–small-cell lung cancer (NSCLC), the most common include inframe deletions of exon 19 (~45%) and the exon 21 L858R (~40%). Clinical trials have ascertained that the oral EGFR tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, lead to superior response rates (RRs) and progression-free survival (PFS) than standard chemotherapies in these NSCLCs.[1,2] The reported RRs to gefitinib/erlotinib exceed 70%, with median PFS of approximately 9 to 12 months and overall survival times beyond 20 to 24months.[1] Other less-prevalent *EGFR* mutations, such as the exon 18 G719X (~3%) and the exon 21 L861Q (~2%) display RRs that exceed 50% and prolonged PFS in gefitinib/erlotinib-treated patients.[3] *EGFR* exon 20 insertion mutations (~5%) are associated with preclinical and clinical resistance to gefitinib/erlotinib.[4]

Other less-common *EGFR* mutations have not been completely characterized. This is the case of the exon 18 deletion/insertion mutation delE709_T710insD. Herein, we report the response to erlotinib of an *EGFR* delE709_T710insD mutated NSCLC, and provide a review of the literature on the pattern of response to EGFR TKIs of this mutation type.

CASE REPORT

An 88-year-old white woman with a never-smoking history presented with stage IV NSCLC (adenocarcinoma) with multiple pulmonary nodules, an osteolytic rib lesion, and metastatic lymph nodes. Her Eastern Cooperative Oncology Group performance status was 0. The tumor, obtained from a transbronchial left lower lobe biopsy, did not contain an *ALK* translocation by fluorescence in situ hybridization. Tumor-derived DNA was genotyped (using dideoxynucleotide sequencing) and found to have wild-type *KRAS* and the *EGFR* delE709_T710insD exon 18 mutation.

The patient was started on erlotinib 150 mg/day but was only able to tolerate this dose for 3 weeks. Because of intolerable rash, gastrointestinal symptoms, and anorexia, the dose was reduced to erlotinib 75 mg/day. At the latter dose, the patient continued to have a characteristic EGFR-TKI–induced rash that was tolerable. Imaging studies after initiation of erlotinib demonstrated significant improvement of the patient's tumor lesions (Fig. 1). Measurement of target lesions indicated that the best response was a reduction of 47% in the sum of the largest diameter of the target tumors' dimensions, which classifies as a partial response (PR) using Response Evaluation Criteria In Solid Tumors (RECIST) criteria. The last imaging study was obtained at the 4-month mark of therapy, and the clinical response was maintained for the 6 months of follow-up. However, the patient decided to discontinue erlotinib at the 6-month mark of therapy. Further follow-up for clinical and radiographic progression was censored at that time point.

Frequency of *EGFR* delE709_T710insX among *EGFR* Mutated NSCLCs

We next evaluated the frequency of *EGFR* delE709_T710insX mutations in the Wellcome Trust Sanger Institute Catalogue Of Somatic Mutations In Cancer (COSMIC) online database (http://www.sanger.ac.uk/perl/genetics/CGP/cosmic?action=bycancer&coords=AA%3AAA&start=1&end=1211&ln=EGFR&sn=lung&display=Apply) of *EGFR* mutations in lung cancer as of March 13, 2012. *EGFR* delE709_T710insD was only identified in five of 9539 (0.05%) *EGFR* mutated NSCLCs and delE709_T710insX (insA/insG/insD) in seven of 9539 (0.07%) *EGFR* mutated NSCLCs.

Response of *EGFR* delE709_T710insD to EGFR TKIs

Two additional cases of patients whose tumors harbored *EGFR* delE709_T710insD and who received gefitinib have been reported.[3,5] The calculated disease-control rate to EGFR TKIs for the *EGFR* delE709_T710insD cohort was 66% (2 of 3 cases), and in two patients (including the case reported here), the PFS exceed 4 months. One of the cases was reported twice with divergent responses; in one publication as a PR[5] and in another as stable disease to gefitinib 250 mg/day[3]; in both the PFS was reported as 5 months. We assume this case had significant tumor regression but only met criteria for an

Department of Medicine, Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.
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Address for correspondence: Daniel B. Costa, MD, PhD, Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA 02215. E-mail: dbcosta@bidmc.harvard.edu

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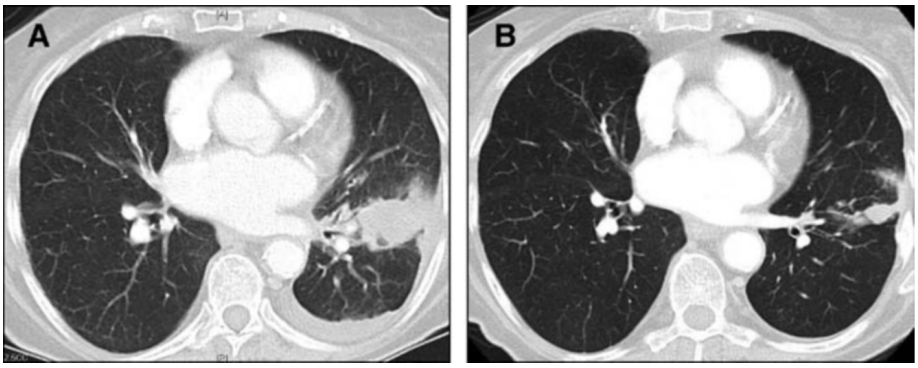

FIGURE 1. Computed tomography images of the thorax of an adenocarcinoma of the lung harboring the *EGFR* delE709_T710insD mutation (*A*) before and (*B*) after erlotinib. EGFR, epidermal growth factor receptor.

unconfirmed PR by RECIST criteria. The other case had progressive disease as best response to gefitinib 250 mg/day with a PFS of 0.9 months.[3] These data indicate that the majority of NSCLCs with *EGFR* E709_T710delETinsD had tumor regression upon exposure to EGFR TKIs.

DISCUSSION

EGFR delE709_T710insD exon 18 mutations account for less than 0.1% of previously reported *EGFR* mutations in NSCLC. Our case and the two additional cases reported in the literature provide evidence that *EGFR* delE709_T710insD may lead to enhanced sensitivity to reversible EGFR TKIs. In vitro studies will be needed to confirm this assertion. The clinical observation that patients with tumors with this mutation achieved radiographic tumor regression may be indicative that other patients with *EGFR* delE709_T710insD bearing tumors can benefit from gefitinib and/or erlotinib at their usual clinical doses. In summary, *EGFR* delE709_T710insD is a rare but potentially EGFR-TKI–responsive mutation in NSCLC. The case presented here will be added to the Vanderbilt's DNA-mutation inventory to refine and enhance cancer treatment database (http://www.mycancergenome.org/direct.php), with the goal of enhancing the ability of oncologists to select therapies for patients with uncommon *EGFR*-mutated NSCLCs.[6]

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