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EGFR delE709_T710insD: a rare but potentially EGFR inhibitor responsive mutation in non-small-cell lung cancer

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Keywords

lung cancer; non-small-cell lung cancer; EGFR; EGFR mutation; erlotinib; gefitinib; tyrosine kinase inhibitor; delE709_T710insD; E709_T710delETinsD

Introduction

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 survivals (PFSs) than standard chemotherapies in these NSCLCs (1;2). The reported RRs to gefitinib/erlotinib exceed 70%, with median PFSs of ~9-12months and overall survival times beyond 20-24months (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, methods and results

Case report

An 88-year-old white Caucasian female with a never smoking history presented with stage IV NSCLC (adenocarcinoma) with multiple pulmonary nodules, an osteolytic rib lesion, and metastatic lymph nodes. Her ECOG performance status was 0. The tumor, obtained from a transbronchial left lower lobe biopsy, did not contain an *ALK* translocation by FISH.

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Tumor-derived DNA was genotyped and found to have wild-type *KRAS* and the *EGFR* delE709_T710insD exon 18 mutation (using dideoxynucleotide sequencing).

The patient was started on erlotinib 150mg/day but was only able to tolerate this dose for 3 weeks. Due to intolerable rash, gastro-intestinal symptoms and anorexia the dose was reduced to erlotinib 75mg/day. At the latter dose, the patient continued to have a characteristic EGFR TKI-induced rash that was tolerable. Imaging studies following initiation of erlotinib demonstrated significant improvement of the patient's tumor lesions (Figure). 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 RECIST. 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 COSMIC online database of *EGFR* mutations in lung cancer as of March 13th 2012 (http://www.sanger.ac.uk/perl/genetics/CGP/cosmic?action=bycancer&coords=AA%3AAA&start=1&end=1211&ln=EGFR&sn=lung&display=Apply). *EGFR* delE709_T710insD was only identified in 5/9539 (0.05%) *EGFR* mutated NSCLCs and delE709_T710insX (insA/insG/insD) in 7/9539 (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 that received gefitinib have been reported (3;5). The calculated disease control rate to EGFR TKIs for the *EGFR* delE709_T710insD cohort was 66% (2/3 cases), and in our current report and another patient 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); and in both the PFS was reported as 5 months. We assume this case had significant tumor regression but only met criteria for an unconfirmed PR by RECIST. 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 2 additional cases reported in the literature provide evidence that *EGFR* delE709_T710insD may lead to enhanced sensitivity to reversible EGFR TKIs. Confirmatory *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 (DIRECT) 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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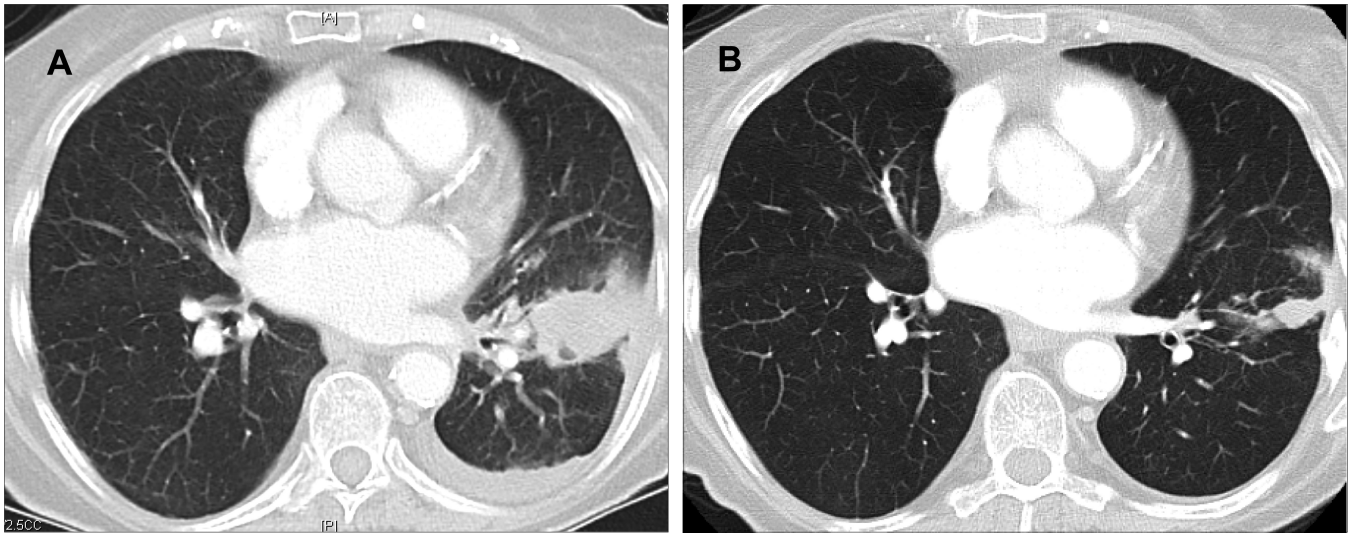

Figure.
Computed tomography images of the thorax of an adenocarcinoma of the lung harboring the *EGFR* delE709_T710insD mutation before (A) and after (B) erlotinib.