Activity of Gefitinib in a Non–Small-Cell Lung Cancer Patient with Both Activating and Resistance EGFR Mutations

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INTRODUCTION

Tyrosine kinase inhibitors (TKIs) of epidermal growth factor receptor (EGFR) can be considered the standard first-line therapy of patients with advanced non–small-cell lung cancer (NSCLC) harboring activating EGFR mutations. Despite an initial response to TKIs, the development of secondary resistance leads to treatment failure.[1] Various mechanisms have been reported to be associated with acquired resistance to EGFR–TKIs, including the presence of the exon 20 T790M mutation that produces resistance to TKIs by increasing the affinity of the EGFR to ATP.[2,3] Therefore, patients harboring the exon 20 T790M mutation are generally considered to be resistant to reversible TKIs (gefitinib or erlotinib).[4] We report a case of a long-lasting response to gefitinib in an advanced NSCLC patient, harboring both an activating and a "resistance" *EGFR* mutation.

CASE REPORT

On June 1, 2010 a 72-year-old man, formerly a light smoker, was admitted to our institution for a lung lesion of the left lower lobe, with mediastinal lymph nodes, and lung, hepatic, and bone metastases (Fig. 1A). The Eastern Cooperative Oncology Group performance status was 2. A liver biopsy was positive for a large-cell carcinoma, TTF-1 and CK-7 positive. EGFR mutational analysis performed by polymerase chain reaction/sequencing and the Qiagen Therascreen EGFR Mutations Kit (Qiagen, Milan, Italy) showed three different mutations in the tumor, as confirmed by two independent analyses: c.2236–2250 deletion in the exon 19, producing the aminoacidic deletion p.E746-A750; c.2369C>T mutation in exon 20 (*p.T790M*); c.2573T>G (*p.L858R*) point mutation in exon 21. The difference in threshold cycle between the control and the mutation-specific assays (ΔCt) suggested that the three mutations were not equally represented in the tumor, and that alleles carrying the c.2236–2250 deletion (ΔCt 0.31) were more abundant as compared with the *T790M* mutation (ΔCt 3.28), with the *L858R* showing the lowest levels of mutant alleles (ΔCt 5.90) (Fig. 2). On these bases, on August 11, 2010, the patient was started on therapy with gefitinib 250 mg/day, after completing radiotherapy on bone sites. On September 20, 2010, a partial response to gefitinib was observed, with a reduction of the left lung lesion, hepatic metastases, and disappearance of the bilateral lung nodules (Fig. 1B). The treatment was continued without significant toxicity until April 30, 2011, when a lung and liver progression of disease was observed. Gefitinib was stopped and the patient was switched to gemcitabine as single agent for six cycles.

DISCUSSION

It has been demonstrated using highly sensitive techniques that up to 35% of NSCLC patients with an activating *EGFR* mutation also carry clones of tumor cells with the *T790M* mutation, which is not detectable using routine diagnostic tests.[5] Our patient showed a peculiar mutational profile, with three different mutations, but the *T790M* mutation was present only in a fraction of cells harboring sensitizing mutations, explaining the long response to gefitinib (8 months). Therefore, the presence of a *T790M* mutation with an activating *EGFR* mutation should not be considered as a contraindication to first-line therapy with TKIs in advanced NSCLC patients. Our data also suggest that relative quantification of mutant alleles might provide information useful for treatment decision.

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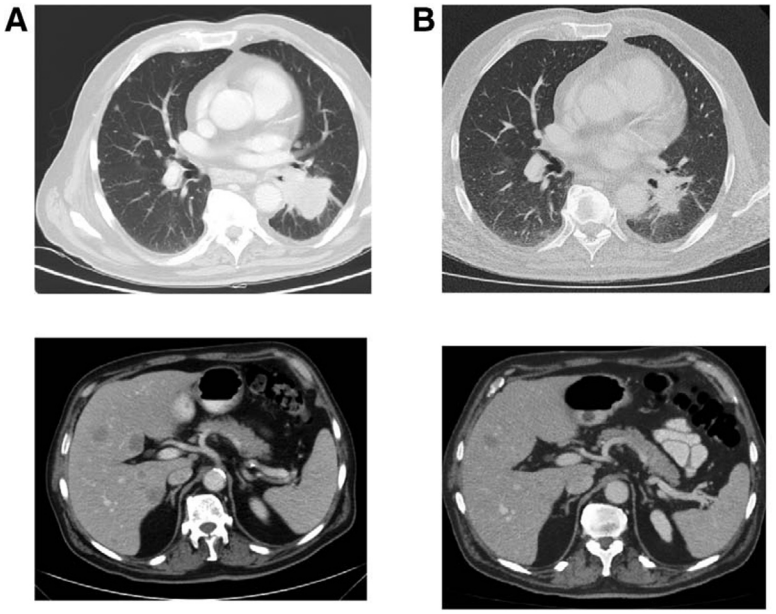

FIGURE 1. Computed tomography scan (*A*) at diagnosis and (*B*) after 1 month of therapy with gefitinib.

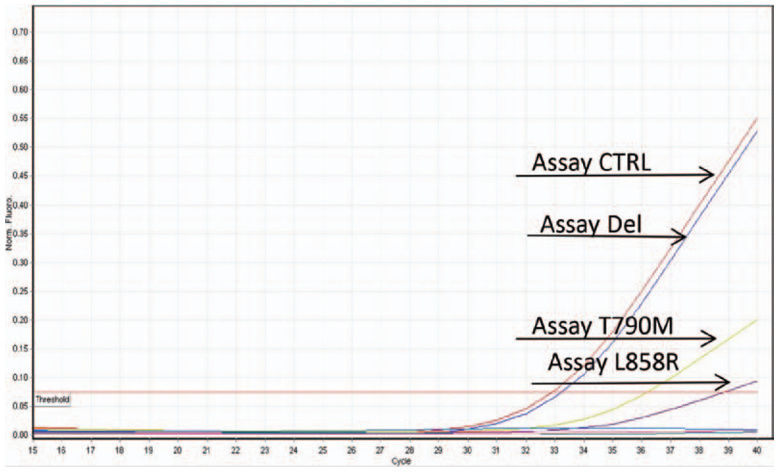

FIGURE 2. Analysis of EGFR mutations with the Qiagen Therascreen EGFR Mutations kit. EGFR, epidermal growth factor receptor.

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