EGFR mutation in gefitinib-responsive small-cell lung cancer

Activating mutations within the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) underlie responsiveness to gefitinib in non-small-cell lung cancer (NSCLC) [1–3]. To date, however, only a few EGFR mutations have been detected in other solid tumors [4]. We now describe a patient with gefitinib-responsive small-cell lung cancer (SCLC) who harbors a deletion in exon 19 of EGFR.

A 72-year-old woman with no history of smoking presented with a 2-week history of cough, dyspnea and intermittent hemoptysis. Computed tomography (CT) revealed a mass in the upper lobe of the right lung and a large metastatic mass in the liver. Bronchoscopy revealed a tumor occluding the right upper bronchus and bronchoscopic biopsy was performed. Treatment with 250 mg of gefitinib once daily was initiated at the patient’s request. Her symptoms improved rapidly, with CT performed 3 weeks after the initiation of gefitinib treatment revealing marked regression of both the primary lung tumor and the metastatic liver tumor. Histological examination of the transbronchial biopsy specimens showed that the tumor comprised small cells with round or oval nuclei (Figure 1A). The final pathological diagnosis was thus SCLC and was confirmed independently by three additional pathologists. Positive staining of the tumor cells for neural cell adhesion molecule (CD56), a sensitive and specific marker of neuroendocrine differentiation, supported the pathological diagnosis. Further immunohistochemical analysis revealed expression of EGFR in the tumor cells (Figure 1B). Direct sequencing of the region of EGFR that encodes the kinase domain (exons 18 to 21) in DNA isolated from tumor biopsy specimens identified a heterozygous in-frame 15-base pair deletion that resulted in the loss of amino acids 746 to 750 (delE746-A750) (Figure 1C). This mutation is identical to a previously described deletion in exon 19 of EGFR in NSCLC [1–3]. The mutation in the proband was detected in both sense and antisense sequences of the products of two independent polymerase chain reactions.

In contrast to NSCLC, EGFR expression has been reported to be low in SCLC. Gefitinib was recently shown to inhibit EGFR signaling in SCLC cell lines that express the receptor even at a low level [5], however, suggesting the presence of functional EGFRs in SCLC. As far as we are aware, ours is the first report of an EGFR mutation in a patient with SCLC, a finding that suggests that EGFR tyrosine kinase inhibitors may be a treatment option for a subset of SCLC tumors that express functional EGFRs.

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Figure 1. EGFR expression and mutation in tumor tissue at diagnosis of gefitinib-responsive SCLC. (A) Hematoxylin–eosin staining showed that the primary tumor was composed of small cells with round or oval nuclei and sparse cytoplasm. (B) Immunohistochemical analysis showed expression of EGFR in tumor cells. (C) Nucleotide sequencing of EGFR in tumor DNA revealed a heterozygous in-frame deletion within the region of the gene encoding the tyrosine kinase domain (double peaks).

references


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