Treatment Resistant *de novo* Epidermal Growth Factor Receptor (EGFR)-mutated Small Cell Lung Cancer

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Small cell lung cancer (SCLC) is an aggressive high-grade bronchogenic carcinoma with neuroendocrine features occurring predominantly in current or former smokers.1 Despite initial sensitivity to platinum-based chemotherapy, almost all patients will relapse and develop resistance to conventional treatment.2 At present, no effective targeted treatment strategies have been approved in SCLC.3 In contrast, oncogenic driver mutations in epidermal growth factor receptor (EGFR) are detected in up to 33.1% of non-small cell lung cancers (NSCLC)4 and predict response to EGFR-targeted tyrosine kinase inhibitors (TKIs).5 However, the presence of EGFR mutations has been reported in SCLC, existing either *de novo* or in cases of transformed EGFR-mutant (mt) adenocarcinoma. Whilst phenotypic SCLC transformation is a known acquired resistance mechanism to EGFR-TKI agents, treatment responses in the *de novo* setting are rarely described and remain largely unknown.

We report a rare case of a female patient, who had never smoked, with *de novo* EGFR-mt SCLC and describe the treatment outcomes to both platinum chemotherapy and erlotinib.

**Case report**

An 84-year-old Caucasian female with no smoking history was diagnosed with stage IV small cell lung carcinoma (T3N1M1b) after initially presenting with a respiratory tract infection. Past medical history included osteoarthritis and hemicolectomy for early stage bowel cancer 12 years prior. Computed tomography (CT) of the chest, abdomen and pelvis demonstrated a 4 × 2.3 × 2.4 cm left upper lobe mass with adjacent rib invasion, left hilar lymphadenopathy, bilateral pulmonary nodules and a solitary 1.5 cm liver metastasis. In accordance with institutional guidelines, cerebral imaging was not used to evaluate for the presence of intracranial metastases as part of her staging workup due to the patient being asymptomatic. Endobronchial ultrasound fine needle aspiration of station 11L node showed poorly differentiated carcinoma with neuroendocrine features, immunohistochemistry positive for thyroid transcription factor 1 (TTF-1), synaptophysin and CD56, and Ki67 index of 50–60% – features most in keeping with small cell carcinoma. No adenocarcinoma component was seen on histology. Molecular testing was undertaken on both the original tumour tissue and plasma due to the patient’s history of never smoking. Molecular testing on tumour tissue included Sanger sequencing-based EGFR mutation screen and next generation sequencing (NGS) analysis targeting 24 commonly mutated lung cancer oncogenes utilising the Illumina platform. Circulating free (plasma) DNA was tested using the Cobas® EGFR plasma assay (Roche, Basel, Switzerland) to detect the presence of common activating mutations in EGFR exons 18, 19 and 20 and 21. An activating exon 19 deletion EGFR mutation was detected in both tumour and plasma. NGS analysis detected additional somatic mutations in TPS3 and PKI3CA.

Epidermal growth factor receptor (EGFR) mutations are a rare occurrence in small cell lung cancer (SCLC), existing either *de novo* or in cases of transformed EGFR-mutant (mt) adenocarcinoma. In the *de novo* setting, treatment outcomes and response to EGFR-tyrosine kinase inhibitors is unclear. We report a rare case of a female patient, who had never smoked, with *de novo* EGFR-mt SCLC and describe treatment outcomes to both platinum-based chemotherapy and erlotinib. Considering the rarity of EGFR mutations reported in SCLC and the unclear role of EGFR-tyrosine kinase inhibitors in this setting, a review of the literature will also be presented.
At the time of diagnosis, the patient reported cough, fatigue and chest wall discomfort from rib erosion. Her Eastern Cooperative Oncology Group (ECOG) performance status was 3 due to disease-related symptoms. Treatment with single agent carboplatin area under curve (AUC) 6 every 3 weeks was selected in the setting of poor performance status. In accordance with institutional guidelines, restaging CT scan following four cycles was carried out, which confirmed platinum-refractory progressive disease with multiple new pulmonary metastases, progressive nodal and liver metastases. Second-line erlotinib was initiated with dose reduction (100 mg once daily). The patient experienced a G1 acneform rash responding to antihistamines and topical emollients. Following 8 weeks of erlotinib, the patient reported increasing chest wall pain. Restaging CT scan confirmed further disease progression at the site of the primary tumour and liver, and erlotinib was subsequently stopped. Due to significant chest wall pain, the patient received 20 Gy in 5 fractions palliative radiotherapy to the left chest wall. No further lines of treatment were initiated due to decline in performance status. The patient was referred for best supportive care in the community and died 11 months from the date of her initial diagnosis.

Discussion

The presence of $de$ $novo$ $EGFR$ mutations in SCLC is a rare occurrence. Incidence ranges from 0.2–4.0% in the reported literature with an association with females with a lower accumulated smoking dose (pack-years). In a review of 53 reported cases of $EGFR$-mt SCLC, 53% (n=28/53) presented with a $de$ $novo$ diagnosis of SCLC.

$EGFR$ mutations commonly observed in $de$ $novo$ $EGFR$-mt SCLC included exon 19 deletions (43%) and L858R mutations (31%), similar to $EGFR$-mt adenocarcinoma. However, in one Chinese cohort of patients with SCLC, $EGFR$ exon 18 (G719X) mutations was most frequently detected over $EGFR$ exon 19 del and $EGFR$ L858R mutations. Rarer mutations in DBB5H and LB61QQ have also been detected. Whilst current guidelines do not recommend routine molecular testing for $EGFR$ mutations in SCLC; screening for such mutations may be considered in cases with combined small cell/adenocarcinoma history or in cases with clinical factors favouring the presence of an $EGFR$ mutation such as younger age, light smoking history or East Asian ethnicity. The implications of $de$ $novo$ $EGFR$-mt SCLC with regards to patient outcomes are not well established. In particular, there are limited and differential reports to response to $EGFR$-TKI agents. Treatment outcomes in published cases of $de$ $novo$ $EGFR$-mt SCLC without an adenocarcinoma component are presented below.

A number of cases report initial responses to first-line chemotherapy in $de$ $novo$ $EGFR$-mt SCLC without exposure to $EGFR$-TKI agents. In their case series of SCLC in never-smokers, Kurahara et al. reported a 65-year-old female with co-mutations in $EGFR$ L858R and $KRAS$ G12A. Partial response to carboplatin/irinotecan was achieved; however, the patient died 16 months after diagnosis. Shiao et al. described a 63-year-old male with a heavy smoking history with $EGFR$ exon 19 del SCLC with partial response to platinum/etoposide. The patient relapsed within 2 months and died 10 months after diagnosis. Siegela et al. presented a case of a 68-year-old Caucasian never-smoking female with $EGFR$ L858R mutation SCLC. The patient was treated and responded to several lines of chemotherapy. Thai et al. reported on two Asian patients with $de$ $novo$ $EGFR$ L858R mutant SCLC. One 73-year-old male who had never smoked achieved complete response following definite chemoradiation whilst the other 66-year-old female patient who had never smoked but had extensive-disease SCLC died 1 month after single-agent carboplatin was commenced. None of the above patients were exposed to an $EGFR$-TKI.

Okamoto et al. reported the only case demonstrating response to first-line gefitinib in $de$ $novo$ $EGFR$ exon 19 del SCLC in a 72-year-old female patient who had never smoked. However, duration of response and subsequent lines of therapy were not described.

In the vast majority of case reports, $de$ $novo$ $EGFR$-mt SCLC has been resistant to $EGFR$-TKI therapy. Shiao et al. reported on a 54-year-old female, who had never smoked, with $EGFR$ exon 19 del limited-disease SCLC with partial response to concurrent chemoradiation. The patient died 17 months after diagnosis after failing to respond to topotecan, doxorubicin, gefitinib and etoposide all given sequentially as single agents. Asai et al. described a 68-year-old never-smoking female with $EGFR$ exon 19 del SCLC. She initially responded to platinum-etoposide then amrubicin. On relapse she was given third-line gefitinib which resulted in progression. With similarities to our reported case, Varghese et al. and Le et al. both described separate cases of never-smoking females with $de$ $novo$ $EGFR$-mt SCLC. Both patients were resistant to platinum/etoposide and progressed rapidly on second-line erlotinib. Similarly to the present case, an additional $PIK3CA$ mutation was detected in the case by Verghese et al.

The differential lack of response to $EGFR$-TKIs observed in the majority of $de$ $novo$ SCLC compared to $EGFR$-mt NSCLC or mixed SCLC/NSCLC may indicate that an $EGFR$ mutation is not the primary oncogenic driver in high-grade differentiated tumours or that underlying mechanisms of resistance exist. A number of hypotheses may explain treatment-resistance in $EGFR$-mt SCLC, acknowledging larger series are required before drawing firm conclusions. Le et al. observed lack of $EGFR$ protein expression even in the presence of genomic $EGFR$ mutations in SCLC, postulating that dysregulated translation of $EGFR$ from DNA/RNA to protein results in reduced TKI response. Of interest, acquired mutations in $PIK3CA$ in $EGFR$-mt NSCLC may result in resistance to $EGFR$-TKI therapy. Both the present case and Verghese et al. describe similar clinical outcomes with disease refractory of platinum-based chemotherapy and subsequent erlotinib in the presence of a known $PIK3CA$ mutation, hypothesising that this mutation is a potential resistance mechanism in $EGFR$-mt $de$ $novo$ SCLC as well. In $in$ $vitro$ studies of NSCLC, gefitinib-resistant cell lines confirm that the presence of $PIK3CA$ mutation, which results in continued activation of the PI3K signalling pathway, is sufficient to override gefitinib-induced apoptosis, conferring gefitinib resistance. In a small retrospective series exploring the impact of concurrent $PIK3CA$ mutations in $EGFR$-mt NSCLC, shorter median overall survival was observed in patients with concurrent $EGFR$ and $PIK3CA$ mutations versus $EGFR$-mt/$PIK3CA$ wild type (wt) patients (18 months versus 33 months; p=0.006). Although a notable numerical difference between $EGFR$-mt/$PIK3CA$-mt versus $EGFR$-mt/$PIK3CA$-wt NSCLC was observed with regards to duration on TKI therapy at 2 years (0% versus 34%) in addition to progression-free rate at 2 years (0% versus 20%) and 3 years (0% versus 7%), no significant difference in objective response rates to $EGFR$-TKI therapy was observed. This does raise the possibility that concurrent $PIK3CA$ is a negative prognostic factor in $EGFR$-mt lung cancer as opposed to a direct resistance mechanism; however, the retrospective nature and small sample size (n=42) limits definitive conclusion. Overall, further characterisation of mutational spectrum in $EGFR$-mt SCLC, particularly in the $de$ $novo$ setting, is required to define other resistance mutations and better define treatment algorithms in this rare and select group.
In summary, we present a rare case of de novo EGFR-mt SCLC with PIK3CA mutation refractory to platinum-based chemotherapy and erlotinib. A summary of published treatment outcomes in reported cases of pure de novo EGFR-mt SCLC suggests poor responses to EGFR-targeted agents. Future studies to document clinical outcomes of these patients and define potential treatment resistance mechanisms will help further define the utility of EGFR-TKI agents in these patients.