Editorial Commentary

Is transformed small cell lung cancer (SCLC) different from *de novo* SCLC?

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Small cell lung cancer (SCLC) transformation is one of the mechanisms for acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (*EGFR*-TKIs) in non-small cell lung cancer (NSCLC) (1-5). Although two types of histology are commonly thought to be different diseases, Oser *et al.* suggested that both combined histology tumors and SCLC transformation are possible because the type II alveolar cells, which are the cells of origin of some *EGFR*-mutant adenocarcinomas (ADC), may be transformed into SCLC (1). SCLC transformation from ADC has been sometimes observed in *EGFR*-wild type lung cancers that lack other mutations (6,7) or during anaplastic lymphoma kinase (*ALK*)-targeted therapy (8-10) and programed cell death-1 (PD-1) immunotherapy (11,12). In addition, SCLC transformation has sometimes been reported in cancers other than lung cancer probably as a result of frequent repeat biopsies (13,14).

However, whether such transformation occurs from NSCLC to SCLC, or whether the cancer originates from the coexistence of both, remains controversial (1,15,16). A Korean cohort study that utilized longitudinal sequencing may help understand the clonal evolution and genetic predictors of SCLC transformation (16). The authors investigated 21 patients with stage IV *EGFR*-mutant ADCs that had transformed into SCLC. Whole genome sequencing was carried out for 9 tumors from 4 patients at various time points. The clonal evolution to *EGFR*-TKI resistant SCLC occurred early, even before the use of *EGFR*-TKI. Furthermore, the inactivation of both *RB1* and *TP53* was observed from the early time point in serial repeat biopsies. In addition, the analysis of mutational signature revealed that the apolipoprotein B mRNA editing catalytic polypeptide-like (APOBEC)-induced hypermutation was frequent in branches leading to SCLC transformation. In another study, several researchers investigated the Rb and p53 expression in the original NSCLC tissue without *EGFR* mutation from a patient with SCLC transformation when the patient was undergoing treatment (7). In both the original NSCLC and transformed SCLC, Rb and p53 were completely inactivated. Therefore, the assessment of *RB1* and *TP53* in *EGFR*-mutant NSCLC could help predict the emergence of SCLC transformation, and inactivation of these two genes may warrant close monitoring during *EGFR*-TKI and subsequent treatments.

Although histological transformation to SCLC occurs in approximately 3% to 10% of *EGFR* mutant NSCLC cases (17-19), the natural history and clinical course of SCLC after transformation from NSCLC are poorly understood. Initial case reports and systematic reviews indicated that the prognosis of transformed SCLC is poor and standard chemotherapy for *de novo* primary SCLC seemed to be ineffective (5,13,20). However, more recent studies have reported favorable outcome after systemic chemotherapy (6,18). A retrospective analysis sought to characterize disease features and outcomes of *EGFR*-mutant SCLC and other high-grade neuroendocrine carcinomas (18). The majority of patients (87%) had NSCLC at initial diagnosis, whereas 9 (13%) had *de novo* SCLC or a mixed

histology. All patients had *EGFR* mutations at diagnosis (exon 19 deletion in 67%, L858R in 24%, and *de novo* T790M in 3%), and those with NSCLC had been treated with at least one *EGFR*-TKI. The median time to SCLC transformation was 17.8 months. The most common mutations associated with transformation to SCLC included *TP53* (79%), *Pb1* (58%), and *PIK3CA* (27%). Platinum-etoposide was associated with an overall response rate (ORR) of 54% and a median progression-free survival (PFS) of 3.4 months. Notably, among the 17 patients who received immunotherapy with PD-1 or PD-L1 inhibitors, there were no responders and the diseases progressed rapidly in all patients. Taxane chemotherapy was the most common treatment for patients progressing on platinum-etoposide chemotherapy, and was associated with an ORR of 50% and a median PFS of 2.7 months. Central nervous system metastases occurred in 64% patients following transformation to SCLC. The median overall survival (OS) from diagnosis was 31.5 months, and median OS from transformation was 10.9 months.

SCLC transformation in non-*EGFR*-mutant NSCLC is rarely reported. This phenomenon might be partly owing to the limited use of repeat biopsy in clinical practice (6,18). A recent multicenter retrospective study of 48 *EGFR*-mutant and 13 non-mutant NSCLC cases between 2005 and 2017 analyzed patient survival (6). The median time to the transformation was significantly shorter in the *EGFR*-mutant group than in the non-mutant group (16 *vs.* 26 months, P=0.01). Although the ORR of chemotherapy was similar to around 40–45%, the OS from the initial diagnosis was significantly worse in the *EGFR*-mutant group compared to the non-mutant group (28 *vs.* 37 months, P=0.06). However, the OS from the time of transformation was not different (9 *vs.* 10 months, P=0.56). Molecular analyses revealed that 32 cases (84%) of *EGFR*-mutant tumors retained the same mutation after SCLC transformation. In three cases of initial *EGFR* exon 19 deletion, the transformed SCLC was associated with *PI3K* mutation + *c-MET* amplification (one case), *ALK* fusion alone (one case) and *ALK* fusion + *EGFR* exon 21 + exon 18 mutations (one case). One case of initially *EGFR* exon 19 deletion observed both exon 19 deletion and exon 20 T790M after SCLC transformation. These findings suggest that these mutations could be found in the SCLC transformed cells or also in other NSCLC cells. This variety and heterogeneity of driver mutations could be a point of difference between transformed SCLC and *de novo* SCLC.

As increase in numbers of patients treated with osimertinib in the *EGFR*-TKI resistant or naïve setting, new mutations and other mechanisms of resistance are emerging. SCLC transformation could occur solely or combined with other mutations, as an acquired resistant mechanism similar to first- and second-generation *EGFR*-TKIs (21). However, its incidence and configuration with other resistance mutations are still being investigated. From a therapeutic perspective, several clinical cases of SCLC transformation after osimertinib treatment were reported to respond well to platinum-based doublet chemotherapy (4). *In vitro*, osimertinib-resistant cells with SCLC transformation were more sensitive to paclitaxel compared with osimertinib-sensitive cells (22,23). Therefore, repeat biopsy even in patients resistant to osimertinib could help optimize the subsequent treatments.

In summary, transformation to SCLC occurs in a small but important subset of patients with *EGFR*-mutant NSCLC (18). This phenomenon might be explained either by a phenotypic switch from NSCLC to SCLC histology, or a combination of SCLC and ADC that may be present at baseline, with SCLC becoming the main component during therapeutic course (6). Histological transformation to SCLC may have more aggressive behavior in the *EGFR*-mutant group because the median time to transformation is significantly shorter in this group than in the non-*EGFR*-mutant group. However, this might be biased by the recommendation of repeat biopsy in *EGFR*-mutant patients after a line of targeted therapy, whereas this is not recommended in non-*EGFR* mutant NSCLC (6). SCLC transformation may be suspected in NSCLC patients who clinically deteriorate during targeted therapy or immunotherapy (3,9,24). In this clinical setting, repeat biopsy is highly recommended to rule out SCLC transformation because platinum-etoposide chemotherapy yields impressive responses in cases of transformed SCLC, like *de novo* SCLC. Several research efforts are focused on trying to assess SCLC transformation by the use of non-invasive biomarkers such as serum pro-gastrin-releasing peptide, neuron-specific enolase (3,9,24) and liquid biopsy. Furthermore, molecular investigations with a larger cohort may be necessary to better understand the clonal evolution in transformed SCLC and to design an optimal subsequent treatment after *EGFR*-TKI in *EGFR*-mutant NSCLC.

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Footnote

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