Third-generation tyrosine kinase inhibitor in the treatment of epidermal growth factor receptor mutated squamous cell lung cancer: a tailored therapy approach

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Abstract: We reported the case of a male patient suffering from a metastatic squamous cell carcinoma, harboring a complex inframe deletion in exon 19 of epidermal growth factor receptor (EGFR), treated with erlotinib and osimertinib and subsequently with immunotherapy. A 54-year-old male, with a light smoking history, presented in October 2015 with metastatic squamous cell lung cancer (SqCLC). Deletion p.E746_S752>V in EGFR exon 19 was found and after progression to erlotinib treatment, the liquid biopsy-based re-assessment highlighted a p.T790M EGFR mutation. Osimertinib was then started. After 5 cycles disease progression was detected and nivolumab was started. A subsequent clinical and radiological progression occurred after 3 nivolumab administrations. Next-generation sequencing (NGS) analysis, performed on metastatic tissue, confirmed the original EGFR deletion and showed also the presence of EGFR p.G724S and TP53 p.P152L mutations. Patient died in December 2017. The reported case highlighted tumor's molecular features prominent role over histology, offering further insights about druggable mutations in SqCLC. Furthermore, we confirm the emerging role of EGFR p.G724S mutation as a Osimertinib resistence mechanism.

Keywords: Epidermal growth factor receptor mutation (EGFR mutation); immunotherapy; squamous cell lung cancer (SqCLC); precision medicine; third-generation tyrosine kinase inhibitors

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Introduction

Activating mutations of epidermal growth factor receptor (EGFR) are present in about 3–4% of squamous cell lung cancer (SqCLC). EGFR testing is, therefore, not routinely recommended unless in never or former light smokers (1). Tyrosine kinase inhibitors (TKIs) are nevertheless an effective treatment in SqCLC harboring activating mutations of EGFR (2). Herein we report the case of a patient suffering from a metastatic SqCLC, harboring a complex inframe deletion in exon 19 of EGFR, treated with erlotinib and osimertinib, and subsequently with immunotherapy.

Case presentation

A 54-year-old male, presented in October 2015 with metastatic SqCLC. Transbronchial biopsy showed a p63 and p40 positive, thyroid transcription factor 1 (TTF-1) negative phenotype. Taking in account the current non-smoking status of the

patient and his light smoking history (three packs per year), in accordance with the last ESMO recommendations (2), an EGFR assessment was prescribed. Due to the rapid drop in clinical conditions, a first line therapy with cisplatin plus gemcitabine was started concurrently. The molecular analysis was performed through the myriapod lung status kit (Diatech pharmacogenetics) on a Mass-ARRAY system. Deletion p.E746_S752>V in EGFR exon 19 was highlighted. Neither ALK nor ROS-1 rearrangements were found. BRAF mutational status was not assessed. Disease progression occurred after two cycles of chemotherapy. Therapy with erlotinib 150 mg daily was consequently started. The CT scan showed a lung progression after 6 months. No significant side effects were reported. The liquid biopsy-based re-assessment by Real Time PCR confirmed the exon 19 deletion and highlighted a p.T790M EGFR mutation. Osimertinib was then started, within the ASTRIS clinical trial, a real world treatment study of osimertinib in patients with EGFR T790M positive non-small cell lung cancer (NSCLC) (3). Best response to both TKIs was partial response according to RECIST 1.1 criteria. A lung lesion progression was detected after five cycles, nivolumab was started after bronchial re-biopsy. Both the squamous histotype and EGFR deletion were confirmed, while the p.T790M mutation was no longer detectable. BRAF mutations in exon 15 were not found. PDL-1 expression was not evaluated on this biopsy, lacking enough tissue for the analysis. Due to the onset of buccal rhymes deviation, a brain CT scan was performed after three cycles of nivolumab demonstrating brain metastatic involvement. Based on both patient's characteristics and treatment history, a re-challenge with erlotinib was attempted, but progression occurred after 2 months and docetaxel was started. Skin involvement occurred after three cycles and the treatment was therefore stopped. Skin biopsy was PDL-1 negative and Next-generation sequencing (NGS) analysis utilizing the Oncomine solid tumor DNA kit (Thermo scientific), showed in the *EGFR* gene the persistence in exon 19 of the sensitizing p.E746_S752>V mutation (allele frequence 56%) together with a mutation in exon 18, p.G724S (allele frequence 25%). A TP53 p.P152L mutations (allele frequence 70%) was also found. Other three missense mutations in three different genes at <1% allele frequencies were identified. ALK and ROS-1 were not rearranged and BRAF mutations in exon 15 were not present. No clinical trials being available, supportive care was implemented. Patient died in December 2017.

Discussion

The reported case highlighted tumor's molecular features prominent role over histology, offering further insights about druggable mutations in SqCLC. For SqCLC patients checkpoint inhibitors showed convincing evidence of efficacy (4), and current guidelines do not routinely recommend EGFR characterization. However, the clinical case we presented suggests histology paradigm may be overwhelmed by tumor's molecular characterization.

Furthermore, we confirm the emerging role of EGFR p.G724S mutation, as a Osimertinib resistence mechanism (5). The increasing evidence of additional actionable mutations and the constantly growing knowledge of potentially targetable acquired resistance mechanisms, combined with the growing scalability of high throughtput technologies, will enable clinicians to better tailor both target treatments and immunotherapy (6), leading to a true precision medicine.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: No informed consent could be signed by the patient for this specific manuscript because he died in December 2017, before we have begun this work. We tried to contact his wife but she has never answered our calls. Nevertheless, identifying information are not published in this work and patient's anonymity is absolutely guaranteed.

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