Editorial Commentary

Uncommon EGFR mutations in non-small-cell lung cancer

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Introduction

The advent of targeted therapies has radically changed the treatment landscape of advanced non-small-cell lung cancer (NSCLC) harboring oncogenic drivers. Epidermal growth factor receptor (EGFR) mutations represent the main molecular target occurring in approximately 10–15% of Caucasians and up to 50% of Asian patients. They are strongly associated with adenocarcinoma histology, female sex, young age and no-smoking status (1).

The two most common EGFR mutations are Exon 19 deletion and L858R exon 21 point-mutation of the tyrosine kinase domain of the gene. They are termed classic mutations and account for more 85% of cases. The remaining 10–15% of patients present uncommon EGFR mutations consisting of a heterogeneous group characterized by different clusters within exons 18–21 (2,3). Their incidence could be underestimated due to the low sensitivity of the conventional methods used in clinical practice. Indeed, according recent evidences, the increasing use of modern techniques as next-generation sequencing (NGS) might expand and improve their detection (4). It is strongly recommended that uncommon EGFR mutations be adequately tested because they represent therapeutic targets with significant implications for treatment-decision (5).

EGFR tyrosine kinase inhibitors (TKIs) are the standard of care for patients with EGFR-mutated NSCLC. Several agents have been developed including first- (erlotinib, gefitinib), second- (afatinib, dacomitinib) and third-generation TKIs (osimertinib). These agents showed highly better efficacy and safety outcomes compared to chemotherapy in randomized clinical trials. Recent head-to-head clinical trials have shown that second- and third-generation TKIs are more effective than first-generation agents (6,7). In particular, the phase III FLAURA trial has demonstrated the significant superiority of Osimertinib over gefitinib and erlotinib in terms of efficacy, safety profile and overall survival in untreated NSCLC patients harboring EGFR mutations (8).

However, most pivotal trials, including the FLAURA, enrolled only patients with classic EGFR mutations. The activity of EGFR TKIs on uncommon mutations have been assessed in retrospective studies, post-hoc analysis, case reports or small prospective series. Therefore, given the lack of a large prospective trial, controversies remain (9).

The complex scenario of uncommon EGFR mutations

The uncommon EGFR mutations are part of a highly heterogenous group including hundreds of variants mostly being in the exons 18–21 of the gene encoding tyrosine kinase domain.

Exon 18 mutations account for 3–4% of all EGFR mutations and consist of mainly point mutations in the codons 719 (especially G719X) or 709 (E709X). Deletions and insertions are extremely rare. A peculiar association

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with male sex and smoking history has been described, as opposed to other EGFR mutations (10).

Deletions are the most frequently mutations identified in exon 19, including at least 30 different variants, but most of them are usually missed by commercial available Kits for EGFR testing used in clinical practice (11). Exon 19 insertion and missense mutation are rare and clinical data are lacking.

Exon 20 insertions are the most prevalent among uncommon mutations accounting over 5% of EGFR-positive NSCLC cases. As well as classic mutations, they are associated with female sex, Asian ethnicity e no-smoking habits, but on the contrary, they are classically considered drug-resistant EGFR mutations, although a high level of heterogeneity exists (12).

T790M substitution in exon 20 represent the main mutation of acquired resistance to first- and second-generation TKI in case of classical EGFR mutations. Uncommon mutations showed a lower incidence of acquired T790M mutations and is very rare as single point mutation in naive patients. It is strongly predictor of response to Osimertinib (13).

The S768I substitution in exon 20 and the L861Q mutation in exon 21 are two of the major uncommon mutations exhibiting differential sensitivity to EGFR TKIs. They have a similar incidence, both occurring in 1–2% of EGFR mutated cases and are often compounded with other mutations (14).

The coexistence of multiple EGFR mutations, termed as compound or complex mutations, usually consist of one classical sensitizing mutation together with a rare partner mutation or co-occurring uncommon mutations. Complex mutations are classically considered a rare event. However, the application of new mutational testing techniques, such as multiple PCR system and NGS, significantly increased the cases with complex mutations, occurring in up to 14% of all EGFR-mutated NSCLC (15).

A number of extracellular domain mutations in exon 2–15 and other rare uncommon mutations have been identified, but the clinical significance is not well yet characterized (16).

Globally, the prevalence of uncommon EGFR mutations is similar to other molecular drivers such as BRAF mutations, ROS1 and ALK re-arrangements. However, the molecular diagnostics currently used in clinical practice do not provide an accurate and comprehensive EGFR profiling. As a result, uncommon mutations can be undetected. In light of the different clinical significance, the heterogeneity and variable responses to the TKI, the treatments choices can be biased. Therefore, detection and treatment of the uncommon EGFR mutations represent areas of unmet need, requiring the implementation of the modern molecular diagnostic tools and the appropriate decoding of the literature evidences.

Therapeutic evidence

Treatment of NSCLC with uncommon EGFR mutations is still a debated and controversial issue. Generally, patients harboring uncommon mutations have a clinically variable response to TKIs and shorter survival rates than classical mutations. However, they display different sensitivity profiles to these agents. Favorable responses were observed in patients harboring G719X, S768I and L861Q, which are classified as sensitizing EGFR mutations. Second- and third-generation EGFR TKIs should be preferred over first-generation TKIs that have shown limited activity (17).

The inclusion of patients with uncommon EGFR mutations in LUX-Lung 2, LUX-Lung 3 and LUX-Lung 6, allowed for a combined post hoc analysis providing prospective evidence that afatinib is strongly active, especially in case of G719X, S768I and L861Q mutations. In this group, median progression-free survival (mPFS) was 10·7 months and median overall survival (mOS) was 19.4 months (18). Low response rate was observed in patients with exon 20 insertions and T790M tumors. These findings supported the use of Afatinib in patients with point mutations or duplication in exons 18–21 but not in those harboring exon 20 insertions or T790 mutation. Moreover, a database of 693 patients treated with Afatinib represents the most comprehensive evidence of the clinical outcomes and activity of a TKI in NSCLC harboring uncommon EGFR mutation. In this study Afatinib confirmed strong activity against major uncommon mutations (G719X, L861Q, S768I), other rare mutations and compound mutations with the exception of those including T790M (19). Based on these findings, FDA has approved afatinib for uncommon EGFR mutation positive NSCLC.

Efficacy of Osimertinib has been investigated in small sample sizes, but increasing evidences derive from phase II trials and real-world observational studies. A multicenter, single-arm, prospective phase II trial tested efficacy and safety of osimertinib in 37 patients harboring rare EGFR mutations. High response rate and long PFS (8.2 months) were observed in major uncommon mutations (G719X, S768I and L861Q) (20). In a multi-center, international, retrospective study, Osimertinib showed activity with

85% disease control rate for NSCLC patients harboring uncommon EGFR mutation, mainly G719X, T790M and L861Q (21). Moreover, Osimertinib represents the most effective TKI in patients with *de-novo* or acquired T790M tumors; instead, limited data are available on its activity against compound mutations and exon 20 insertions.

Exon 20 insertions are considered insensitive to TKI and remain a therapeutic challenge despite recent data showed promising activity of specific agents such as Poziotinib, Mobocertinib and Amivantamab (22). In phase I–II trials, these agents have shown efficacy in pretreated patients reaching an overall response rate of up to 30–40% and disease control rate over 11 months (23). Poziotinib is an orally available quinazoline-based EGFR inhibitor, binding both EGFR and HER2. ZENITH20 trial focused on clinical activity against EGFR ins20, but diverged from previous acknowledgements for high rates of skin and GI toxicities. Mobocertinib emerged for its high inhibition selectivity rate on EGFR ins20 over wild-type compared to other TKIs, yet in preclinical Ba/F3 models. Amivantamab is a bispecific antibody targeting both EGFR and c-MET. Its efficacy is due to the contemporary binding of EGFR and MET, granting a synergistic inhibitory effect, for various EGFR ins20 mutations likewise in EGFR canonical driver mutant NSCLC cell lines, as interconnected downstream signaling pathways are simultaneously targeted (23). To date, pending results in naive patients, Poziotinib, Mobocertinib and Amivantamab should be considered as treatment options after progression from 1st-line chemotherapy. Ongoing studies are testing the efficacy of new drugs as Luminespib and Tarloxotinib (23).

Emerging evidence suggest that uncommon mutations may be sensitive to immune checkpoint inhibitors (ICIs). Immunotherapy plays a marginal role in EGFR-positive NSCLC, but it is still not well explored in patients harboring uncommon mutations. Association with smoking history, high level of programmed death ligand-1 (PD-L1) expression and tumor infiltrating lymphocytes (TILs) were found in rare EGFR-mutated NSCLC compared to classical EGFR mutations (24). These findings encourage further studies for the assessment of potential benefit from ICIs. Chemotherapy has limited activity and should be considered only in case of EGFR drug-resistant or no targetable mutations.

In conclusion, it is clear that identifying EGFR mutational profile is crucial for clinical decision-making (25). There is no consensus on treatment strategy in NSCLC patients harboring uncommon EGFR mutations. They represent a highly heterogeneity group showing a variable profile of response to TKIs. Osimertinib and afatinib are frontline agents for patients with uncommon major mutations including G719X, S768I and L861Q. Osimertinib is effective in 790M-positive tumors, while afatinib is not. However, afatinib has accumulated more evidence in the cases with other sensitive mutations, including complex mutations. The exon 20 insertion represents EGFR-TKI-resistant mutation but is the target of novel specific agents such as mobocertinib, amivantamab and poziotinib. Based on the limited evidence available in literature, therapeutic decisions should be made on a case-by-case basis.

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