Although it can be expelled spontaneously,[7] an invasive method may be required when the needle cannot be reached by bronchoscopy. Otherwise, the needle may perforate or migrate to the vascular system or cause chronic inflammation as a response to a foreign object. Only in 7 of the 22 cases reported did the needle break after the adenopathy was punctured [locations 7 (3 patients), 4L (2), 4R (1) and 10R (1)]. The potential causes of needle breakage include[7]: (1) tangential position of the needle due to the angle required for puncture; (2) harder than usual cartilaginous rings or lymph nodes; (3) manufacturing defects of the needle. To prevent this complication, excessive angulation of the needle should be avoided and its structural integrity should be checked prior to each puncture. The needle can also break and remain retained within the sheath.[8] In this case, when the sheath is extracted from the working channel and the stiffening wire is inserted, the broken distal end of the needle will be expelled. Needles generally break prior to the procedure.

The lesson learned from this experience is that, although EBUS is a safe technique, complications – such as transbronchial puncture needle breakage – may arise. The structural integrity of the needles should be checked throughout the procedure and upon completion. The needle must be extracted. If it cannot be recovered by conventional bronchofibroscopy, an invasive method will be required.

Abbreviations

EBUS   endobronchial ultrasound
EBUS-TBNA   endobronchial ultrasound with real-time
                guided transbronchial needle aspiration

Authors' contributions

VR, AG and LV were responsible for the conception and design of the study, and wrote and edited the manuscript. AC contributed to the drafting and revision of the manuscript. All authors read and approved the final manuscript.

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Treatment of advanced EGFR-mutant NSCLC patients: Sequencing matters

Dear Editor,

The availability of several treatment options in epidermal growth factor receptor mutation-positive (EGFR M+) non-small cell lung cancer (NSCLC), poses a challenge for clinicians as to what to consider when choosing the best treatment sequence?

First, a fast and comprehensive mutation screening is required to define subpopulations benefiting from target therapies, which should include, at present time, at least EGFR, ALK, ROS1 and BRAF genes.[1]

Table 1 EGFR TKIs profile.

	Mechanism of action	Advantages	Disadvantages
1G EGFR TKI	Blocks the activity of the tyrosine kinase receptor by reversibly binding the adenosine triphosphate site	Higher efficacy than chemotherapy Better toxicity profile than platinum-based chemotherapy	Unknown benefit in uncommon mutations Lack of efficacy in presence of T790M mutation Limited data on CNS activity
Erlotinib Gefitinib		Allows dose adjustments	Does not allow dose adjustments
2G EGFR TKI	ErbB family irreversible inhibitors	Higher efficacy than chemotherapy and 1G EGFR TKI Allows dose adjustments	Lack of efficacy in presence of T790M mutation
Afatinib		Higher efficacy than 1G EGFR TKI Proven efficacy even with dose reductions Approved for uncommon mutations Low hepatic toxicity/Less drug-to-drug interactions Activity in CNS BM	Requires dose management due to the toxicity profile
Dacomitinib			Unknown activity in the SNC and in uncommon mutations
3G EGFR TKI Osimertinib	Developed to specifically and irreversibly target T790M mutation Lower activity against wild-type EGFR	Efficacy in presence of T790M mutation CNS activity Less toxicity/Fewer severe AEs	Heterogeneous resistant mechanisms OS not yet known

1/2/3G, first/second/third generation; BM, brain metastases; CNS, central nervous system; EGRF, epidermal growth factor receptor; OS, overall survival; RR, response rate; T790M, substitution of a threonine (T) with a methionine (M) at position 790 of exon 20; TKI, tyrosine kinase inhibitors; TTF, time to treatment failure.

Choosing the first-line treatment should take into account several clinical and drug-related factors, such as pharmacological profile, efficacy, toxicity and progression mechanisms. Also, the first-line option will influence the treatment sequence.

There are currently several first-line treatment options available for EGFR M+ NSCLC patients, known as first (1G), second (2G) and third-generation (3G) EGFR tyrosine kinase inhibitors (TKIs) (Table 1).

Several phase III trials demonstrated superior efficacy of erlotinib (OPTIMAL, EURTAC, ENSURE), gefitinib (First-SIGNAL, IPASS, WJTOG3405, NEJ002) and afatinib (LUX-Lung 3, LUX-Lung 6) versus standard platinum-based chemotherapy.[2] Toxicity profile and quality of life were also superior.[3]

Two head-to-head trials (LUX-Lung 7 and ARCHER 1050) compared the efficacy and safety of 1G and 2G TKIs. In the LUX-Lung 7, afatinib showed superior efficacy over gefitinib considering progression free survival (PFS), time-to-treatment failure (TTF) and the objective response rate (ORR). Also, a positive, but not statistically significant, trend was observed on overall survival (OS), favouring afatinib.[4,5]

The phase III ARCHER 1050 trial compared dacomitinib to gefitinib in the first-line setting, excluding patients with brain metastases (BM).[6] Dacomitinib showed benefit on PFS and OS; however, no differences were found in ORR between groups.[6,7]

More recently, the FLAURA trial compared 3G osimertinib and 1G EGFR gefitinib and erlotinib.[8] Osimertinib, in the first-line setting, showed better PFS, longer median duration of response and higher, although not statistically significant, ORR.[8] At data cut-off, OS data was immature. Until now, there are no comparative data with 2G TKIs.[8]

Most of the evidence about EGFR rare mutations, which represent 10–15% of patients,[9] comes from afatinib studies, where afatinib showed efficacy in patients with advanced-stage lung adenocarcinomas harbouring non-classical mutations, specifically on S768I, L861Q and G719X mutations.[10]

Another important clinical factor for first-line treatment decision is the central nervous system (CNS) activity and the presence of BM. Data on the direct intracranial activity of 1G TKIs is limited.[9] Regarding 2G, afatinib demonstrated efficacy in patients with asymptomatic BM and delayed CNS progression[9]; no data is available on dacomitinib.[9] Osimertinib demonstrated activity in patients with BM at standard therapeutic doses, and a reduction in CNS progression was also demonstrated.[9]

EGFR TKIs are associated with a class-related adverse event (AE) profile due to wild-type EGFR inhibition. Although afatinib is associated with a higher percentage of severe AEs, it is well demonstrated that the availability of several doses allows dose adjustments that do not compromise drug efficacy; therefore, the discontinuation rate due to AE was similar between afatinib and gefitinib on the LUX-Lung 7 study.[2,4,5,8] Additionally, afatinib undergoes minimal hepatic metabolism and is not a substrate for liver primarily via cytochrome P450 (CYP)-dependent enzymes, having, therefore, a lower probability for drug interactions.[9]

Despite EGFR TKIs proven efficacy, inexorable disease progression still occurs. For patients with oligometastatic progression, the treatment strategy can be to keep the EGFR TKI, and local radiotherapy should be considered; for systemic progression, treatment should be changed.[3]

The most common mechanism of resistance related to 1G and 2G TKIs is the acquisition of the gatekeeper mutation in EGFR T790M, which occurs in 50–70% of cases.[9]

At the time of disease progression, EGFR T790M mutation can be detected through liquid biopsy or tissue rebiopsy.[11] If the T790M is not present in the liquid biopsy, a tissue rebiopsy should be performed.[11]

Since rebiopsy may present some challenges (patients may refuse or not be eligible, progression may occur in an inaccessible location), the use of a highly sensitive liquid biopsy technique, which allows higher percentage of detection and a high agreement rate with the tissue biopsy, may maximise the detection of patients with T790M mutation and, therefore, the number of patients benefiting from osimertinib as a second-line treatment.[12]

Although a high sensitivity technique for the detection of the T790M mutation is not yet accessible in all hospitals, for hospitals with access to this technique, the choice of first-line therapeutic option may rely on therapeutic sequencing.

Resistance mechanisms to osimertinib present great variability and appear to be heterogeneous, with lack of specific therapeutic options after its use.[2,9]

Therapy sequencing is a critical point. If the first option is a 1G or 2G TKI, in patients with clinically relevant progression and confirmed T790M+, osimertinib is the second-line standard of care.[11] Updated OS data from LUX-Lung 7 shows that sequential therapy with afatinib followed by a 3G EGFR TKI, namely osimertinib, was effective, with a 3-year OS rate up to 90%.[5,13]

For patients T790M-negative, after progression following 1G or 2G TKI, therapy sequencing is, for now, not applicable, and chemotherapy is the current standard treatment.[2]

If osimertinib is used in first-line treatment, we can guarantee access for patients that might not be able to use it in 2nd line after progression with a different mechanism than T790M, or patients without the opportunity of a 2nd line.

We are still waiting for mature data on OS and PFS2 after first-line treatment with osimertinib.[8]

Unfortunately, to date, after progression, the standard of care for these patients is only platinum-based chemotherapy. There are many ongoing trials assessing agents that target specific mutations or combinations.[2,9,11]

With the recent approval from the European Medicines Agency of the combination chemotherapy + atezolizumab + bevacizumab, a new door has opened.

There is no single therapeutic solution for the first-line treatment of NSCLC patients with EGFR M+: depending on the patient's profile and on the access to the liquid biopsy technique that allows the detection of the T790M resistance mutation, the first-line therapeutic option will vary between sequencing approach or the use of a 3G EGFR TKI in 1st line. Optimised EGFR TKI sequencing might be the most critical determinant of OS in patients with activating EGFR mutations. Data on OS from clinical trials and real-life cohorts will help us to understand the best sequence for each individual patient.

Conflicts of interest

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