Diagnosis and treatment of non-small cell lung cancer: current advances and challenges

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In this editorial we will discuss several interesting and timely topics which are relevant for current thoracic oncological practice. First, we will address epidermal growth factor receptor (*EGFR*) mutations and resistance, followed by ground glass opacities (GGO), current diagnostic assessment tools including patient derived organoids (PDO), assessment of circulating tumour DNA (ctDNA) and circulation tumour cells (CTC). Finally, we will also address a complex case of delayed extensive chest wall infection following a lobectomy via thoracotomy.

The treatment of advanced non-small cell lung cancer (NSCLC) has traditionally been via the systemic administration of platinum-based chemotherapy. Overall survival (OS) is poor with only 33% at 1 year and 11% at 2 years (1). With the discovery of *EGFR* mutations, new treatment pathways emerged. These mutations are primarily found in lung cancer with an adenocarcinoma component, non-squamous NSCLC, young Asian women (<50 years) and non or light smokers (2). In these patients, if systemic treatment is considered, molecular testing including *EGFR* mutations need to be assessed. Selective tyrosine kinase inhibitors (TKI) of EGFR (EGFR-TKI) were developed

to target *EGFR* mutation harbouring NCSLC. Via EGFR stimulation, the tyrosine kinase (TK) pathway has a role in cell proliferation and migration, apoptosis evasion, and angiogenesis pathways. In case of *EGFR* mutated NSCLC activation, this will lead to overstimulation of the EGFR and cause tumour growth.

Initial first generation inhibitors of the EGFR-TK pathway, in the form of gefitinib, erlotinib and icotinib were promising. Monotherapy with gefitinib showed an overall response rate (ORR) of 71.2% *vs.* 47.3% when compared to platinum-based chemotherapy as demonstrated in the IPASS trial (3). Yet the ORR in the population lacking an *EGFR* mutation was a mere 1.1% (gefinitib group) *vs.* 23.5% (carboplatin-paclitaxel group). In the WJTOG345 trial, gefitinib was compared to docetaxel and cisplatin in patients with *EGFR* mutated NSCLC, demonstrating an ORR of 62.1% *vs.* 32.2% (4). Erlotinib, another first generation EGFR-TKI has been used in the first-line treatment for *EGFR* mutated NSCLC patients. It showed a progression-free survival (PFS) of 8.0–13.1 months compared to 4.6–6.9 months in the platinum-based chemotherapy (5). Equally promising was a higher ORR of 58–83% compared

to 15% to 47.3% in the conventional chemotherapy group.

Unfortunately, acquired resistance occurred in about 65% of patients after a period of 9–13 months of treatment, with the gatekeeper *T790M* point mutation being the most common mutation (6). This mutation increases the adenosine triphosphate (ATP) binding affinity leading to ATP outcompeting the first generation EGFR-TKI, negatively affecting PFS. To treat this newly acquired resistance, second generation EGFR-TKI were introduced like afatinib and dacomitinib. These second generation EGFR-TKI have an increased irreversible covalent binding affinity leading to a broader inhibitory profile. They are particularly successful in the presence of *L858R/T790M*-mutant *EGFR*, or mutated *ErbB2*. However, this also leads to increased toxicity due to its simultaneous inhibition of wild type EGFR.

A third generation EGFR-TKI namely osimertinib, has been developed to specifically target mutated *T790M* EGFR via irreversible covalent binding. It was designed to be used in patients with an acquired *T790M* mutation after initial treatment with first or second generation EGFR-TKI. The AURA3 trial confirmed that applying osimertinib following first and second generation EGFR-TKI in patients with confirmed *T790M* mutations increased ORR (71%) compared to platinum-pemetrexed (31%; odds ratio =5.39) (7). In terms of safety and adverse events, fewer patients reported adverse events of grade 3 or more in the osimertinib arm than in the platinum-pemetrexed arm (23% *vs.* 47%). The AIRA3 study showed a PFS of 10.1 *vs.* 4.4 months in the platinum-pemetrexed group (8). Early identification via biopsy is of utmost importance as PFS seems to be reduced with treatment delay after *T790M* mutation confirmation. However, the question arises if it is suitable in the first-line too? The phase 3 FLAURA-trial confirms it to be a valuable first line approach, especially in cases of with central nervous system progression (9). Due to an improved PFS, even in the absence of brain metastases or a lack of *T790M* mutation identification, osimertinib may be considered as first line approach. The case by Zheng *et al.* (10), nicely demonstrates the therapeutic challenges of acquired EGFR-TKIs resistance. The presence of the rare *718Q* mutation identified via next generation sequencing (NGS) leads to osimertinib resistance. In the EGFR resistance group the novel *718Q* mutation still lacks a formal treatment strategy. In the presence of rare mutations the treatment with personalized chemotherapy might render the tumour mass more homogenous, after which third generation EGFR-TKI can be reused since sensitive

cells might again become more dominant and sensitive to this TKI (11).

Early-stage NSCLC should be treated with resection if cardiopulmonary function is adequate. For tumours <5 cm with negative nodes, adjuvant chemotherapy is not recommended when R0 resection was obtained (12). Hence, genetic profiling in early-stage NSCLC is also not routinely performed and its prognostic value is unclear. To identify patients at high risk of relapse, and those that might nonetheless benefit from adjuvant therapy, NGS and PDO can be used. PDO are 3D tumour cultures grown from the resected primary tumour using its tissue specific stem cells. Using the PDO, histological, structural and genetic characteristics could be investigated. By exposing the PDO to EGFR-TKI, dose response curves may help identify the most efficacious drug. Yet, we do not know if using targeted therapy after the identification of genetic abnormalities leads to prolonged OS or PFS as first line therapy. On a broader level, the use of PDO could provide precise genetic molecular data and guide selective drug trials via *in vitro* research.

The ability to identify molecular and genetic changes via liquid specimens without having to obtain tissue samples is also very appealing, as acquiring these samples is easier than obtaining tissue biopsies. The ability to identify potentially actionable gene mutations is promising and would provide a possibly continuous identification of any genomic alterations. This would in turn allow to re-analyse treatment regimens directing further therapy (13). An advantage of ctDNA assessment is the ability to identify tumour heterogenicity, whilst tissue biopsies may fail to do so. It may also assess differences in tumour genetics between primary and metastatic lesions. If the molecular status needs to be obtained, an attempt to acquire ctDNA may be performed. The biggest concern is the low sensitivity despite the high specificity, as the sensitivity depends on identifying ctDNA, which only represents a minimal portion of all free circulating DNA. We therefore need to determine the optimal pre-test conditions and analytic techniques. These problems make it an alternative if tissue biopsy is unobtainable, but not yet a full clinical alternative.

Timing of chemotherapy and targeted therapy re-challenge can be aided by the use of CTCs and ctDNA. This may help in evaluation of therapy effectiveness (14). This alternation of therapy can be performed before radiological changes are apparent, however, prospective studies with this approach still need to be performed to confirm the hypothesis.

In the case of non-actionable mutations, NGS analysis of ctDNA or CTCs should be reserved when resistance to conventional first line chemotherapy occurs. Pharmacogenomic studies might help explain why the sensitivity of NSCLC chemotherapy varies between 20–60% and might shine light on potential predictive markers of chemotherapy effectiveness. Currently, studies have yet to identify such predictive markers in the treatment of lung cancer patients (15).

In the presence of multiple lesions, identifying the lesions as metastatic or synchronous multiple primary lung cancers (SMPLC) is a common diagnostic difficulty. Apart from imaging features, molecular or genomic features may help. Different responses of lesions to chemotherapy or EGFR-TKIs should raise suspicion that the lesions are actually SMPLC or metastases having acquired a new genetic mutation (16). In the case of N1 or N2 metastatic, *EGFR* mutated NSCLC, these patients might benefit from *EGFR-TKI* (17). Yet, the application of systemic chemotherapy could still be a potential benefit to suppress other undetected lesions, possibly extending the PFS. The advantage of salvage surgery in the case of solitary metastases also helps in the identification of SMPLC. The debate then continues whether or not gefinitib should be applied immediately or be reserved if recurrence occurs in close follow-up. Such a case is presented in the article by Zang and colleagues, highlighting the potential role of salvage surgery in the case of N1 or N2 metastatic, *EGFR* mutated NSCLC (18). In the systematic review by Raphael *et al.* (19) EGFR-TKIs as adjuvant therapy after resection of *EGFR* mutated lung cancers, extend PFS, but not OS. Therefore, as a clear benefit in OS has not yet been demonstrated, the use of EGFR-TKI as adjuvant therapy is not yet generalized. In the CTONG1104 trial, an increase in disease-free survival (DFS) was obtained with similar OS after adjuvant gefitinib when compared to standard platinum-based chemotherapy (17). This is also supported by the ADAURA trial (20). In this trial, patients with stage IB, II or IIIA following completely resected NSCLC with positive *EGFR*-mutation received osimertininb or placebo. The trial was however unblinded 2 years early due to a significantly better DFS. All patients had a follow-up of at least 1 year. In the stage II and IIIB population, DFS at 2 years follow-up was 90% in the osimertinib group *vs.* 44% in the placebo group with an overall hazard ratio for disease recurrence or death of 0.17. This 83% reduction in disease recurrence or death showed a highly favourable DFS for patients receiving osimertinib. Due to the premature unblinding, OS could not be calculated from the interim analysis. This trial demonstrates the potential role of osimertinib in adjuvant treatment of *EGFR* mutated NSCLC following complete surgical resection.

Ground glass opacifications continue to pose a challenge as preoperatively obtaining tissue samples remains difficult. Preoperative CT or PET/CT scans are often false negative due to the inactive metabolism and the lack of accompanying positive lymph nodes or distant metasteses (21). Even peroperative identification is difficult due to the lack of a solid mass. Hence, preoperative localization is often mandatory and can be performed via CT-guided techniques using coils, harpoons, methylene blue or indocyanine green. Alternatively, electromagnetic navigation of fluorescent agent for intraoperative localization of GGO and lung nodules can be used (21). Using 3D reconstruction software, a path is planned for an endoscopic approach to the nodules. The electromagnetic sensor probe is advanced up till the closest proximity to the nodule. Subsequently, the probe is changed for a working catheter followed by injection of indocyanine green. This allows for wedge resections and peroperative frozen section examination to determine malignancy of the nodules. The main advantage of transbronchial versus transthoracic localization is the less invasive nature and the possibility to perform localization in the operating theatre, for example, by guiding possible segmentectomy resection margins. Negatively, it comes with high costs and a difficulty to navigate peripheral areas of the lung (21-23).

On a different note, Dai and colleagues present a case of delayed onset of severe culture-negative chest wall infection following a left lower lobectomy via thoracotomy (24). Initial pathology confirmed the presence of bronchiectasis due to an infection with *Aspergillus*. An empyema with wound infection occurred 3 months later which was treated with chest tube drainage. The empyema resolved, however, the wound infection persisted and caused necrosis of sternum and costal arches. Extensive debridement was performed with partial resection of sternum and ribs followed by a lengthy treatment with wet gauze dressings. Unfortunately, no pathogens could be identified despite repeated cultures. This article highlights the diagnostic and therapeutic challenges in extensive necrotic culture-negative chest well infections. Treatment should include antibiotic administration, debridement as necessary, and local dressings. If the debridement is extensive, myocutaneous flaps or synthetic materials when the infection subsides, could be used to improve wound healing. Therefore, radical

resection of the chest wall is challenging as anatomical function needs to be preserved and chest wall reconstruction at a later stage must remain possible. The lack of pathogen identification poses an added challenge for the systemic antibiotic or antifungal treatment. If conventional cultures remain negative, the possibility of genetic sequencing, quantitative polymerase chain reaction or mass spectrometry could be warranted despite its additional cost. For example, the application of such techniques is useful in identifying fungal infections like *Aspergillus*, which was the original pathogen in the presented case (25).

Advances in the field of lung tumour diagnostics, localisation of lung nodules and individualised therapy according to specific mutations or biomarkers follow in rapid succession. The personalised multimodal therapies will create even more complicated, but promising therapies. The necessity of MDT discussions, as featured in this journal, give a good insight in how we can optimise individual patient care and tackle the challenges of novel treatment options including drug resistant tumours.

Acknowledgments

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups. com/article/view/10.21037/jtd-22-364/coif). PEYVS reports institutional fees from AstraZeneca, MSD and Roche. PEYVS is also the unpaid Treasurer of Belgian Association for Cardiothoracic Surgery and unpaid President-elect of International Association for the Study of Lung Cancer. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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