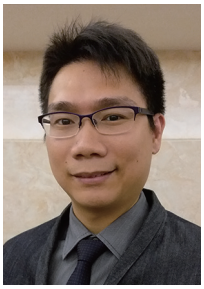
Precision Medicine in Lung Adenocarcinoma



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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 January 2018.

Introduction

With the rapid development in the fields of genetics, biotechnology and genomics, molecular genetic profiling will soon become an indispensable tool for clinicians to guide individualised management of many medical conditions. Precision medicine, also known as personalised medicine, refers to the application of individual patient- and disease- specific profiles, in the light of genetic and genomic data as well as clinical and environmental factors, to assess individual risks and benefits from medical therapies. We take lung adenocarcinoma as an example to illustrate the practice of precision medicine along with anti-cancer therapy.

Lung adenocarcinoma in the past era

The understanding and detection of genomic changes in lung adenocarcinoma evolved dramatically in the past two decades and opened great therapeutic potential for non-small cell lung cancer (NSCLC) patients. Back in the early 1990s, little could be done to distinguish individual subtypes of lung cancers, and most clinical trials focused on finding the best platinum-based combination therapies[1], irrespective of histological subtypes[2,3]. The importance of such differentiation was recognised only later after a large randomised clinical trial had demonstrated in subgroup analysis a survival difference between patients with squamous and non-squamous histology treated with different chemotherapeutic agents[4].

Lung adenocarcinoma in the current era

The development of tyrosine kinase inhibitors (TKI) against epidermal growth factor receptor (*EGFR*) mutated NSCLC opened an era of precision medicine in lung cancer and prompted a paradigm shift towards development of molecularly targeted agents against other putative driver aberrations in NSCLC[5]. Tumours harbouring these distinct and mutually exclusive "driver" mutations can be treated with anticancer therapies largely in the form of TKI that targets respective aberrant gene products. *EGFR* mutations and *ALK* or *ROS1* fusions confer sensitivity to selective kinase inhibitors, which in turn dictate the choice of therapy[5-11]. Additional alterations such as $BRAF^{V600E}$, RET fusions, MET exon 14 skipping, MET and ERBB2 amplifications are found in smaller subsets of patients, but when present may also predict response to some available targeted inhibitors which are FDA-approved therapies for other tumour types[12-16]. In other patients, defined oncogenic drivers such as NTRK and PIK3CA mutations are detected, for which preclinical studies have nominated targeted approaches, but the clinical utility of such therapies has yet to be established[17,18]. In a prospective comprehensive molecular testing of lung adenocarcinoma trial, up to 86.9% (747/860) of patients carry potentially actionable somatic alterations (Fig.1)[19]. The prevalence of these somatic alterations in Asian ethnicity is expected to be higher due to a much higher prevalence of *EGFR* mutations in both never and ever smokers, when compared to studies with patients in majority Caucasian ethnicity[20].

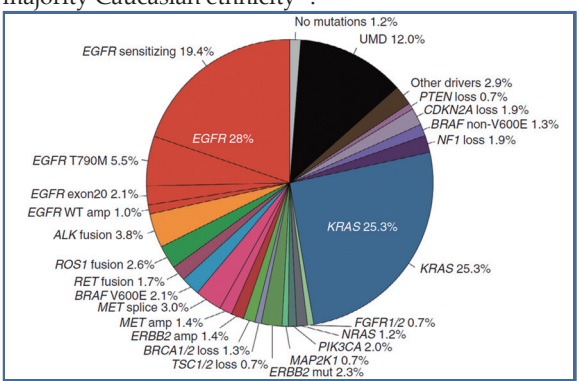

Fig. 1. Potentially actionable oncogenic drivers identified by MSK-IMPACT# testing.
**Figure adopted from reference[19].*
 # MSK-IMPACT: Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets, a hybridization capture-based, next-generation sequencing platform or matched tumor: normal sequencing to comprehensively profile somatic alterations in all known cancer genes in solid tumors.

Somatic mutations detection methods

The aforementioned driver gene alterations can be grouped into three categories – mutations, gene rearrangement, and amplifications – and appropriate molecular testing should be used for detection[21]. A variety of methods can be used for detecting mutations including direct sequencing, real-time polymerase chain reactions, and commercial kits (Table 1)[21]. Fluorescence in situ hybridisation (FISH), immunohistochemistry (IHC), reverse-transcriptase polymerase chain reaction (RT-PCR) and next-generation sequencing (NGS) are options for gene rearrangements, while FISH using a

locus-specific intensifier (LSI) gene and a chromosome-specific centromere (CEP) probe is a standard method for the detection of gene amplifications (Table 1)[21]. Each testing method has to be validated by well conducted clinical trials for corresponding targeted therapies and is often developed as a companion diagnostic under the FDA approved diagnostic framework. However, as targetable genetic alterations are increasingly discovered, individual genotyping may become relatively inefficient, especially when there is inadequate tissue for successive testing, and is drastically costly. NGS technology using DNA or RNA is reported to be useful for multiplexed and deep genomic sequencing[22,23], as well as simultaneously detection of gene rearrangements and genes with copy number gain. Its application allows comprehensive molecular characterisation of lung adenocarcinoma before labelling it as "wild" type, for which no available target therapies can be employed. Nowadays, targeted deep sequencing of selected gene sets (so-called cancer panels) has been integrated into daily clinical practice. Some local diagnostic laboratories have developed platforms for clinicians to order.

Table 1. Representative methods categorized by mechanisms of oncogene activation and by targeted molecules. PCR, polymerase chain reaction; NGS, next-generation sequencing; FISH, fluorescence in situ hybridization; qPCR, quantitative polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction; IHC, immunohistochemistry.
**Table adopted from reference[21]*

Category	Mutation	Gene rearrangement	Amplification
DNA	Direct sequencing PCR-based methods NGS	FISH NGS	FISH qPCR NGS
RNA		RT-PCR (fusion transcript) NGS	
Protein	IHC (mutation-specific antibody)	IHC (protein expression)	IHC (protein overexpression)

Tackling acquired resistance

Despite an initial benefit from molecularly targeted agents in *EGFR*-mutant and *ALK*-rearranged NSCLC, tumours invariably develop acquired resistance and progressive disease. Tumour- or liquid- based re-biopsy at the time of disease progression is valuable for clinicians to understand and tackle the mechanism of acquired resistance accordingly. *EGFR* exon 20 T790M, for example, is the commonest mechanism of resistance after *EGFR-TKI* and can be effectively treated by a third generation T790M mutant specific inhibitor osimertinib[24]. The landmark AURA3 study drives osimertinib therapy a full approval by FDA since Mar 2017 and is currently the only FDA approved therapy after *EGFR-TKI* failure[25]. Non-T790M mediated resistance mechanisms include activation of alternative bypass pathways (e.g. *MET* or *ERBB2* gene amplifications, *IGF-1R* activation, *RET* rearrangement[26]), activation of downstream signalling of the *EGFR* (e.g. *PTEN* downregulation, *CRKL* gene amplification, *BRAF* mutations, or *ERK1/2* reactivation), and phenotypic changes such as SCLC transformation or epithelial to mesenchymal transition (EMT)[27]. Apart from SCLC transformation which should better be treated with etoposide-platinum chemotherapy[28], the vast majority of these resistance mechanisms tell no additional information on the choice of therapy. Empirical cytotoxic chemotherapies usually in the form of pemetrexed-platinum, with or without concurrent antiangiogenic agent, is the only hope to control metastatic lesions in current clinical practice. Nonetheless, the information could be valuable for patients who have exhausted therapeutic options to rationalise the choice of molecular targeted therapies used for other indications in NSCLC or other cancers. For example, monotherapy use of a *MET* inhibitor in *EGFR*-mutant with *MET* amplification as the acquired resistance mechanism has been advocated[29]. The pan-HER dual inhibition trial using afatinib and cetuximab in patients with acquired resistance has shown an objective response rate of 25% among T790M-negative patients[30]. Such dual pan-HER inhibition, which occasionally initiates to *EGFR*-mutant patients who have exhausted all therapeutic options, is only reasonable in acquired mechanisms other than non-HER alternative bypass pathways and EMT phenotypic change, and to a lesser extent, other than downstream signalling activation.

Similarly, the rebiopsy of *ALK*-rearranged NSCLC has provided information on the acquired resistance mechanism of crizotinib and other older generation *ALK* inhibitors (*ALKi*). *ALK* kinase domain "gatekeeper" mutations, including L1196M, C1156Y and G1202R among others, have been observed in around a third of patients after crizotinib resistance[31] and were highly variable after new generation *ALKi* resistance[32]. While L1196M and C1156Y can be effectively treated by ceritinib and alectinib, G1202R confers resistance to most new generation *ALKi* except lorlatinib[32-34]. Lorlatinib remains an investigational agent but could possibly be obtained under a local investigational early access programme with strict patient selection criteria. Alice Shaw et al once demonstrated the beauty of precision medicine through a patient of *ALK*-rearranged lung cancer who had received multiple *ALKi* during the treatment course, including first-, second-, and third-generation inhibitors. The eventually acquired L1198F mutation on tissue rebiopsy conferred resistance to lorlatinib but unexpectedly restored sensitivity to crizotinib[35]. With a rapidly expanding number of new *ALKi*, which include but not exclusively, brigatinib, ensatinib, entrectinib, it is likely that resistance mechanism detected in rebiopies influences the treatment choice in the future era.

Precision immunotherapy in lung cancer

Similar to the advances in targeted therapy, significant progress in tumour immunotherapy has resulted in several new strategies for cancer therapy, including T-cell immune checkpoint inhibitors (ICPI), oncolytic viruses, chimeric antigen receptor T cells, among others[36,37]. Immunotherapy is associated with several unique features, most notably the potential for inducing durable clinical responses, lack of typical drug resistance, and induction of autoimmune-like toxicities. Currently, the immunotherapy in clinical use among lung cancer patients includes pembrolizumab (a PD-1 Ab) monotherapy in highly selected patients with PDL-1

expression over 50% or in combination with pemetrexed-cisplatin regardless of PDL-1 expression in first line situation[38,39], while pembrolizumab, nivolumab (a PD-1 Ab) and atezolizumab (a PDL-1 Ab) monotherapy are utilised as second line treatment after platinum-doublet chemotherapy[40-44]. Of note, most of the landmark trials establishing the role of immunotherapy carry only a small subset or none with *EGFR* or *ALK* mutations and the presence of which were suggested to be associated with lower objective response rate to PD-1 inhibitors. *MET* exon 14 altered lung cancer also carries lower response rate of 6.7% to a PD-1 inhibitor, as reported by Sabari et al at ASCO 2017[45]. Most of these gene alterations are typically associated with a lack of tobacco exposure, an expected lower load of mutation burden, and a lower rate of PDL-1 expression that contributes to the lack of clinical benefit from ICPI. On the contrary, *BRAF* gene aberration and *MET* short variants (SV) mutations are found to be associated with prolonged time on immune checkpoints inhibitor, with *MET SV* linked with increased immune infiltration and an immune activation phenotype[46]. Along with some established roles of microsatellite instability and total mutation burden, comprehensive molecular comprehensive genomic profiling may help further to gauge the degree of benefit from an ICPI in the future era.

Conclusion

The management of advanced lung adenocarcinoma continues to evolve rapidly due to recent advances made in precision medicine diagnostics. The utilisation of comprehensive molecular genotyping allows identification of molecular subgroups of patients with driver mutations who may benefit from molecularly targeted therapies, allows identification of acquired resistance mechanism which may confer sensitivities to newer or alternative molecularly targeted therapies and allows potentially better selection of patients subjecting to immunotherapy. Application of precision medicine diagnostics in the form of NGS, for its methodological complexity, needs extensive trial validation and quality control before implementation into routine clinical use. It would be a tedious and difficult task, but an ultimate goal and a necessary step for all to conquer lung cancer in the future.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Precision Medicine in Lung Adenocarcinoma" by Dr Jacky Yu-chung LI and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 January 2018 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. *MET* exon 14 skipping is one of the potentially actionable somatic alterations.
2. Only up to 30% of lung adenocarcinoma patients carry potentially actionable somatic alterations.
3. The prevalence of *EGFR* mutation among lung cancer patients is higher in Asians than Caucasians.
4. The application of next-generation sequencing allows comprehensive molecular characterisation of lung adenocarcinoma for potentially actionable somatic alterations.
5. Small cell lung cancer transformation is one of the non-T790M mediated resistance mechanisms for *EGFR* mutated adenocarcinoma of lung patients who progress on 1st line *EGFR-TKI*.
6. The spectrum of additional *ALK* domain mutations after *ALK* inhibitors is similar among all newer generation *ALK* inhibitors.
7. The *ALK* G1202R mutation confers resistance to most new generation *ALK* inhibitors except lorlatinib.
8. *MET* exon 14 altered lung cancers have expected excellent treatment outcome to an immune checkpoint inhibitor.
9. Comprehensive molecular comprehensive genomic profiling may help to predict who is likely to respond to immune checkpoint inhibitors.
10. The application of precision medicine diagnostics in the form of NGS is in extensive regional usage, and quality control is not necessary for clinical use.

ANSWER SHEET FOR JANUARY 2018

Please return the completed answer sheet to the Federation Secretariat on or before 31 January 2018 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Precision Medicine in Lung Adenocarcinoma

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Answers to December 2017 Issue

How to Use HIV Pre-exposure Prophylaxis

1. F 2. T 3. F 4. F 5. T 6. T 7. F 8. T 9. T 10. F