Editorial

Molecular biology tools for precision medicine in managing lung cancer

Out of a total of 8.8 million cancer deaths globally, lung cancer was the most common cause of cancer deaths.[1] A 17% increase in cancer deaths was observed over a period of 10 years (2005–2015).[1] Lung cancer is one of the most common cancers in the world and affects more men than women. In 2015, 2 million new cases of lung cancer were recorded globally with 1.6 million deaths.[2] From birth till the age of 79 years, one out of 18 men and one out of 45 women developed lung cancer.[2] In India, the most common cancer was lung cancer followed by stomach cancer.[2]

ADVANCES IN LUNG CANCER DIAGNOSIS

Two new advances need special mention.[3,4] First, the next generation sequencing, to test lung cancer tissue specimen or patient's plasma to identify very minute quantities of various lung cancer mutations. Some of the important lung cancer mutations are epidermal growth factor receptor (EGFR), KRAS, anaplastic lymphoma kinase (ALK), BRAF, RET, MET, phosphatidylinositol 3-kinase (PI3K), human epidermal growth factor receptor 2 (HER2), and ROS1. It is important to realize that lung cancers can be spatially heterogeneous (different mutations in different places in the same tumor) or temporally heterogeneous (different mutations in primary and metastatic tumors) and the proportion of these mutations in a patient with lung cancer can change with treatment. Therefore, it is important to screen for various oncogene drivers present in each patient to first select appropriate treatment as well as during follow-up to identify resistance patterns early so that the treatment can be appropriately modified.[5] An even more sensitive method of testing for mutations is the droplet digital polymerase chain reaction (ddPCR) that can identify mutations even in very low concentrations and has been validated for various mutations in KRAS and EGFR, including the mutation conferring resistance to primary tyrosine kinase inhibitors such as T790M.[6] When obtaining lung cancer tissue with a bronchoscopic biopsy or transthoracic biopsy only a limited area of the tumor is sampled that may not be representative of the whole tumor. The newer sensitive methods such as the NGS and ddPCR use plasma which contains the shed tumor cells and can not only identify the various mutations but also their proportion in each subject. These molecular biology tools can assess changes in these proportions and the presence of newer mutations during treatment [Figure 1, adapted from Tsui and Berger[7]].

GENETIC MUTATIONS IN LUNG CANCER AND PRECISION AND PERSONALIZED ANTI-CANCER THERAPY

It is important that every attempt is made to identify the key oncogene drivers, which are also called as "oncogene addiction genes" to highlight the fact that these tumor cells are dependent on the expression or over-activation of these mutated genes for survival.[3] Efforts are on to

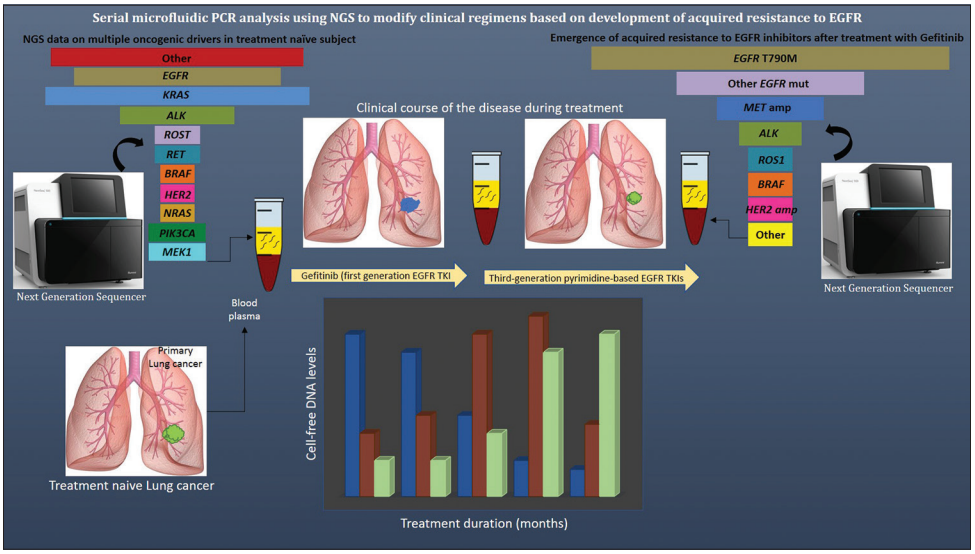

Figure 1: Serial microfluidic analysis using next generation sequencing from plasma utilizing the cell free tumor DNA helps to map out the various mutations, proportions of these mutations and changes in these mutations during the course of treatment of lung cancer

identify drugs that are useful for each of these mutations and are undergoing clinical trials. The classical example is Gefitinib for the EGFR mutations. Other approved drugs against lung cancer with EGFR mutations are afatinib, erlotinib, and osimertinib while Rociletinib is undergoing clinical trials at present.[3] Crizotinib is useful for both ALK and ROS1 translocations and is approved for treatment. There are no other approved drugs for other mutations, but several drugs are under evaluation in clinical trials.[3] Certinib and lorlatinib works for both ALK and ROS1 mutations, vemurafenib, dabrafenib for BRAF mutations, trastuzumab, afatinib for HER2 mutations, trametinib, selumetinib for KRAS mutations, PI3K inhibitors, mammalian target of rapamycin inhibitors for PI3K mutations, crizotinib, tepotinib for MET mutations and cabozantinib, sorafenib, and vandetanib for RET mutations.[3] Identification of highly selective targeted drugs could lead to the development of personalized therapy and precision medicine for patients with lung cancer in the future.

EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS

Epidermal growth factor receptor, a glycoprotein, belongs to the family of tyrosine kinase receptors. On binding to its specific ligand that leads to its phosphorylation, activation of intracellular pathways such as PI3K and AKT, ERK, and JAK/STAT help in cell survival as well as cell proliferation. EGFR gene mutations are found in exons 18–21. The two most common mutations are deletion in exon 19 and L858R substitution in exon 21 that account for more than 80% of all EGFR mutations in lung cancer. Other mutations include insertion in exon 19 and 20, mutations L861 in exon 21 and G719X in exon 18. EGFR mutations such as T790M confer resistance to first-line tyrosine kinase inhibitors (TKIs) such as Gefitinib and Erlotinib and second generation TKI's such as Afatinib and Neratinib but may be susceptible to third line TKI's such as osimertinib and rociletinib. EGFR mutations are more common among Asians than patients from other countries.

Patients with EGFR mutations are associated with around 70% response rates initially to first- and second-line TKI's, but resistance to the drug develops after a median of 9-12 months that leads to the worsening of the lung cancer.[8] The most important mechanism for drug resistance is the development of EGFR T790M mutations (60% of patients).[8] Other mutations such as EGFR D761Y, EGFR 854A, BRAF V600E, NRAS mutations also confer resistance but are not as common. Resistance can also occur through other mechanisms including activation of other pathways (HER2 and MET amplification, fibroblast growth factor receptor activation, programmed cell death-ligand 1 activation, epithelial-mesenchymal transition as well as small cell transformation.[8]

In this issue of Lung India, Amit *et al*.[9] have evaluated whether two common mutations of EGFR (exon 19 deletion and exon 21 mutation) affect survival after treatment with Gefitinib. Although they observed a differential response rates for the two mutations, there were no differences in the progression-free survival and overall survival rates. The authors have not evaluated other mutations or monitored the changes in the mutations during treatment such as EGFR T790M. There is a paucity of survival studies on lung cancer with TKI's in India, and more such studies are needed. An earlier study on survival in India did not evaluate EGFR mutations,[10] followed by a study on EGFR mutations without differentiating between the different mutations on survival.[11] More multicenter studies are needed in the Indian population not only to assess differences between diverse ethnic groups on the molecular biology of lung cancers, the effect of various targeted therapies but also with modified regimens when there is a progression of the disease with newer TKI's. Studies evaluating the effect of TKI's in EGFR mutated lung cancers should in the future dwell on combination therapies to prevent resistance or to modify treatment early based on resistance patterns (using data from next-generation sequencing or digital PCR) to improve survival.

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REFERENCES

1. Mortality GB, Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459-544.
2. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, *et al*. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the global burden of disease study. JAMA Oncol 2017;3:524-48.
3. Calvayrac O, Pradines A, Pons E, Mazières J, Guibert N. Molecular biomarkers for lung adenocarcinoma. Eur Respir J 2017;49. pii: 1601734.
4. Fujii T, Barzi A, Sartore-Bianchi A, Cassingena A, Siravegna G, Karp DD, *et al*. Mutation-enrichment next-generation sequencing for quantitative detection of KRAS mutations in urine cell-free DNA from patients with advanced cancers. Clin Cancer Res 2017;23:3657-66.
5. Paweletz CP, Sacher AG, Raymond CK, Alden RS, O'Connell A, Mach SL, *et al*. Bias-corrected targeted next-generation sequencing for rapid, multiplexed detection of actionable alterations in cell-free DNA from advanced lung cancer patients. Clin Cancer Res 2016;22:915-22.
6. Sacher AG, Paweletz C, Dahlberg SE, Alden RS, O'Connell A, Feeney N, *et al*. Prospective validation of rapid plasma genotyping for the detection of EGFR and KRAS mutations in advanced lung cancer. JAMA Oncol 2016;2:1014-22.
7. Tsui DW, Berger MF. Profiling non-small cell lung cancer: From tumor to blood. Clin Cancer Res 2016;22:790-2.
8. Riely GJ, Yu HA. EGFR: The paradigm of an oncogene-driven lung cancer. Clin Cancer Res 2015;21:2221-6.

9. Joshi A, Patil V, Noronha V, Chougule A, Bhattacharjee A, Kumar R, *et al*. Efficacy of gefitinib in epidermal growth factor receptor-activating mutation-positive nonsmall cell lung cancer: Does exon 19 deletion differ from exon 21 mutation? Lung India 2017;35:32-5.
10. Mahesh PA, Archana S, Jayaraj BS, Patil S, Chaya SK, Shashidhar HP, *et al*. Factors affecting 30-month survival in lung cancer patients. Indian J Med Res 2012;136:614-21.
11. Doval DC, Azam S, Batra U, Choudhury KD, Talwar V, Gupta SK, *et al*. Epidermal growth factor receptor mutation in lung adenocarcinoma in India: A single center study. J Carcinog 2013;12:12.

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