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Molecular Oncology of Lung Cancer! Radiation Oncologist Perspective!!

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Abstract: ***Lung cancer is the leading cause of cancer related death worldwide and Indian population based cancer registry data fully complementing to that, lung cancer histological as well as molecularly is highly heterogeneous disease, previous WHO classification needed to modified by WHO in view of that revised WHO classification based on Immunohistochemistry markers taken up into consideration for lung cancer treatment, prognosis as well as its prediction in this review article will explore all the molecular subtypes of lung cancer along briefly about its specific targeted drugs.***

Keywords: Immunohistochemistry, Targeted drugs, Lung cancer.

1. Discussion

Lung cancer was classified according to previous WHO classification was only based on biopsy or surgical specimen according to that lung cancer divided in two major group NSCLC and SCLC, further NSCLC was divided into squmous cell carcinoma, adenocarcinoma, and large cell carcinoma furthermore squmous cell carcinoma divided into three categories epidermoid type, spindle, and mesothelioma type, and adenocarcinoma was divided into aciner, pappilary, and Bronchoalevoular carcinoma categories, although SCLC was divided into Oat cell, intemidiate, and mixed type verity, however data suggest NSCLC is found 85% of all lung cancer and only 15% are of SCLC.

In the era of IHC when we classify lung cancers in its various molecular subtypes which help us in the decision making of specific targeted therapies in lung cancer IHC study we look for adenocarcinoma, squmous cell carcinoma, Neuroendocrine type lung carcinoma, NUT gene positive lung carcinoma, ALK/EGFR/ROSI/PDL1 subtypes of lung carcinoma, Adenocarcinoma we look for TTF1 (Thyroid transcription factor 1) is a nuclear enzyme and NAPSIN-A if both are present we diagnosed lung cancer as adenocarcinoma, however if we get P40/CK5-6/TP63 lung carcinoma is diagnosed assqumous cell carcinoma, this modification have markedly decreased the proportion of large cell carcinoma which earlier used to diagnosed as large cell carcinoma.

Neuroendocrine types lung cancer:
Neuroendocrine types of lung cancer sub dived into three categories, A-SCLC, B-Large cell Neuroendocrine carcinoma (LCNET) and C-Carcinoid type out of these three categories A and B fall under high grade neuroendocrine types of lung cancer which is very aggressive firm of lung cancer and having poor out come in contract to that of C type means carcinoid type having indolent course of disease.

The NOTCH1 –HESI singling pathway of neuroendocrine tumor formation happens by inactivating INSM1 and ASCL1 are the transcription factor, process starts like NOTCH1 activates HES1 which inactivates INSM1 and ASCL1, INSM1 promotes expression of all three Neuroendocrine markes (CHGA Chromogranin A, SYP Synaptophysin, NCAM1 (CD56) by activating the transcription factor ASCL1 and BRN2.

So finally we could understand that INSM1 appears to be the key factor for the Neuroendocrine differentiation of lung cancer henceforth INSM1 may serve as single most important marker of Neuroendocrine lung cancer differentiation**.**

ALK / ROS1 / EGFR, GENETIC MARKERS:
Various genetic alterations in tyrosin kinase have been identified among Adenocarcinoma of lung cancer ALK (Anaplastic lymphoma kinase) positiveAdenocarcinoma reported to be comprising of 4-5% of all Adenocarcinoma henceforth ALK Inhibitors like Crizotinib, Lorlatinib targeted drugs very helpful for these types of lung cancer, ROS1 (ROS Proto Oncogene-1) positive Adenocarcinoma comprising of only 1-2% of Adenocarcinoma should be considered for ROS1 inhibitor targeted drugs.

EGFR mutants are most common mutations found in Adenocarcinoma of lung cancer, EGFR mutant Adenocarcinoma lung shows TTF1 (Thyroid Transcription Factor 1) immune reactivity along hobnail cell morphology, EGFR mutations divided into four major types of point mutations

1) Point mutations in exon 18.
2) Deletion of exon 19.
3) Insersation in exon 20.
4) Point mutation in exon 21.

Out of above these mutations 90% EGFR mutations in NSCLC SHOES DELETION OD EXON 19 AND POINT MUTATION IN EXON 21, and exon 19 deletion type of lung cancer variety shows superior and prolonged clinical response to EGFR –TYROSIN KINASE INHIBITORS for example Gefitinib or Erlotinib targeted drugs**.**

PDL1 (CD274):
PDL1 (Programmed death ligand-1) which is express on T cells that promotes immunosuppressant action by binding to PD1 on surface of tumor cells actually by binding to PD1 on Cytotoxic T cells thusanti PD1 antibodies inhibit PDL1, thus

allowing immune mediated attacks against tumor cells henceforth using these antibodies for the treatment of NSCLA showing great promise and prolonged survival, particularly NSCLC with 50% or more positivity for PDL1 were associated with higher response rate. Drugs used are Pembrolizumab, Nevolumab and most recently FDA approved (2017) drug is Avelumab

Malignant Mesothelioma:
Mesothelioma is a rare but fatal malignant tumor arising from mesothelial cells and Asbestos exposure considered as major risk factor Mesothelioma sub divided into three histological types, Epidermoid (60-80%), Sarcomatoid (less than 10%), Biphasic (10-15%) loss of BAP1 gene on IHC study as well as deletion of CDKN2A (p16) is a potential indicator of malignant mesothelioma of lung cancer**.**

Nuclear Protein of Testies (NUT) Carcinoma
This type of lung carcinoma recently added in WHO classification of lung cancer which used to misdiagnose more often as deferent type of lung cancer mostly as basiloid type of squmous cell carcinoma or small cell carcinoma, lymphoma, or germ cell tumors.

NUT carcinoma is defined by genetic rearrangement between the nut gene on chromosome 15q14 fused to Bromodomain family member BRD3 on chromosome 19p13.1 (comprising of 70% of NUT carcinoma) and BRD4 on chromosome 9q (comprising of 6% NUT carcinoma) clinically this variety of lung carcinoma shows extremely poor prognosis most aggressive behavior with dismal out come and median overall survival only 2.2 month because this variety do not respond to chemotherapy as well as radiotherapy but somehow molecular targeted therapy against Bromodomain may be beneficial.

Abbreviations:
MM malignant mesothelioma
NSCLC non-small cell lung carcinoma
SCLC small cell lung carcinoma
SqCC squamous cell carcinoma
TKI tyrosine kinase inhibitor

2. Conclusion

In the current WHO classification, immunohistochemical analysis is indispensable to the determination of lung cancer subtypes. Furthermore, immunohistochemical assays have been approved by the U. S. FDA as companion or complimentary diagnostic assays for molecular-targeted therapies. Moreover, an increasing number of targeted therapies will require immunohistochemical evaluation in order to determine the eligibility of patients for certain treatments. Thus, molecular-specific immunohistochemical assays will be performed more frequently to determine specific subtypes, make differential diagnoses, and evaluate relevant biomarkers in lung cancer. Collectively, as part of the current era of precision medicine, immunohistochemical techniques have great promise for improving the diagnosis and treatment of lung cancer.

Conflict of interest: The author declares no conflicts of interest.

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