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Histopathological Variants of Lung Adenocarcinoma: Implications for Targeted Therapy

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Abstract

As the most common type of lung adenocarcinoma, which is the non-small cell lung cancer (NSCLC) subtype, there is considerable variability in histopathology and molecular makeup that influences the prognosis of the patient and their treatment options. This research correlates the targeted therapy responses along with histopathological variants and assesses them with respect to biochemical parameters lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA 21-1), neuron specific enolase (NSE) and circulating tumor DNA (ctDNA) as markers for disease progression and treatment response. A controlled clinical trial was carried out with participants suffering from various subtype adenocarcinomas (lepidic, acinar, papillary, micropapillary and solid variants). Patients received targeted therapy after molecular profiling for EGFR, ALK, KRAS, MET, HER2, and BRAF mutations.

The primary outcomes comprised "progression-free survival (PFS), overall survival (OS) and biochemical marker response." The results captured significant difference among CEA and CYFRA 21-1 concentrations with the burden of the tumor ($p<0.001$), whereas LDH elevation correlated with dismal prognosis and low PFS ($p=0.003$). Further, the change in nanogram of circulating tumor DNA decreased at the end of treatment and it was observed that it had a positive therapeutic response ($p=0.005$) endorsing it as a biomarker for noninvasive approach.The focus of these findings is on the integration of the classification of lung adenocarcinoma with the histopathology and biomarker to improve the approaches of precision medicine.

Keywords: Lung Adenocarinoma, Histopathogical variants, Targeted therapy, Biochemical markers, Precision Medicine

Introduction

Lung adenocarcinoma constitutes the most common type of lung cancer accounting for almost 40% of the total lung cancer cases across the globe[1]. It is noted for itssubstantial diversity in histology, which is directly proportional to the tumors' aggressiveness, their tendency to spread, and response to targeted treatment [2]. The development of modern diagnostics at the cellular level has revealed crucial driver mutations such as epidermal growth factor receptor and anaplastic lymphoma kinase together with Kirsten rat sarcoma viral oncogene homolog, BRAF, MET, HER2, which facilitate in individualized treatment efforts [3]. Although there is progress, the division of molecules into small subsets or groups with no clear homogeneous areas is a problem which signals the need for biochemical markers in order to increase the value of prediction and prognosis.

From the perspective of the histopathology, lung adenocarcinoma is divided into that show lepidic and acinar and papillary, micropapillary and solid subtype patterns, all of which have unique biological behavior [4].

The micropapillary and solid features have been linked with aggressive tumor advancement, elevated recurrence of relapsing cancer, and failure to respond to conventional treatment methods, while lepidic adenocarcinoma is known to have a slow progression pattern. Even though histological grading and molecular profiling forms the basic structure of treatment guiding, there is increasing evidence that biochemical markers such as lactate dehydrogenase, carcinoembryonic antigen, CYFRA 21-1, neuron specific enolase, and circulating tumor DNA provide supplementary information for understanding disease progression and response to treatment.[5]

As an enzyme associated with cellular metabolism, LDH has been shown to be hypoxic and indicative of the tumor's energy metabolism reprogramming, which, adds towards negative prognosis and treatment resistive outcome.[6] Likewise, CEA and CYFRA 21-1 have also been shown to be incorporated in estimating tumor burden and predicting metastatic potential in patients suffering adenocarcinoma while on therapy with the Tyrosine Kinase Inhibitors (TKIs). NSE is an enzyme predominantly expressed in neuroendocrine tumors, has been observed in high concentration in aggressive variants of lung adenocarcinoma, which indicates that its role in metastatic behavior and treatment resistance prediction is important. Additionally, non-invasive evaluation of tumors and their responses to treatment with ctDNA has proven to be an invaluable asset. This research works to determine the relationship that exist between histopathological variants, biochemical markers, and response to treatment with targeted therapies among patients with lung adenocarcinoma.[7-10] This study aims to further improve the strategies of treatment allocation within NSCLC and precision medicine integration through the use of biomarkers, molecular signatures, and histological subtype classifications.

Methodology: Patients diagnosed with lung adenocarcinoma between the years 2021 and 2024 were recruited from Chaudary Pervaiz elahi institute of cardiology, wazirabad for this longitudinal, randomized controlled study. Patients were divided into histopathological subtypes which were lepidic, acinar, papillary, micropapillary, solid variant, and also profiling for EGFR, ALK, KRAS, MET, HER2, and BRAF mutations were done. Depending on the identified mutations, targeted treatments were given either TKI or immune checkpoint inhibitors (ICI), as appropriate. During

the course of the study, Biochemical markers such as LDH, CEA, CYFRA 21-1, NSE, and ctDNA were checked at the beginning, after, and during treatment progression. Secondary outcomes of the study included biochemical response, progression-free survival (PFS), overall survival (OS). Sample size calculation assumed 80% power and 95% confidence interval, using Epi Info software.

Inclusion criteria:

Histopathological diagnosed lung adenocarcinoma

- Driver mutations in either EGFR or ALK, KRAS or MET or HER2 or BRAF.

- ECOG performance status ≤2

Exclusion criteria:

- Small cell lung carcinoma patients

- Systemic chemotherapy within less than 6 months.

- Severe hepatic or renal dysfunction.

This research was approved ethically, and Informed consent was given both orally and in written form.

Table 1: Treatment Response and Biochemical Markers

Parameter	Pre-Treatment (Mean ± SD)	Post-Treatment (Mean ± SD)	p-value
CEA (ng/ml)	15.4 ± 3.2	8.9 ± 2.1	0.002*
CYFRA 21-1 (ng/ml)	4.5 ± 1.8	2.0 ± 1.1	0.001*
LDH (U/L)	210 ± 45	145 ± 36	0.003*

Parameter	Pre-Treatment (Mean ± SD)	Post-Treatment (Mean ± SD)	p-value
NSE (ng/ml)	26.0 ± 5.8	15.2 ± 3.7	0.005*
ctDNA (copies/ml)	90 ± 15	40 ± 10	0.005*

*p < 0.05 indicates statistical significance.

Table 2: Survival Outcomes by Histopathological Variant

Histological Variant	PFS (months, Mean ± SD)	OS (months, Mean ± SD)
Lepidic	18.2 ± 3.5	24.5 ± 4.1
Acinar	14.1 ± 3.2	20.1 ± 3.8
Papillary	12.6 ± 3.0	18.5 ± 3.5
Micropapillary	10.4 ± 2.8	16.2 ± 3.7
Solid	9.2 ± 2.5	14.1 ± 3.0

*p < 0.05 indicates statistical significance.

Discussion

The focus of current research is the effect of histopathological variants as well as biochemical markers on predicting responsiveness to treatment and prognosis in lung adenocarcinoma.[11-14] Our results validate that histopathological variability indeed has a bearing on the behavior of the tumor and its response to targeted therapy. Among the subtypes, micropapillary and solid variants had more aggressive disease with lower progression free survival (PFS) and higher recurrence rates, which is also in line with studies suggesting these patterns are prognostically adverse histologically [16]. On the other hand, lepidic variant had more PFS and responded better to tyrosine kinase inhibitors (TKIs), thus further supporting the relevance of histological subtype on therapy decisions [17].

Biochemical markers (LDH, CEA, CYFRA 21-1, NSE, and ctDNA) were diagnosed in govenal finding participants of these samples and provide theses additional prognostical as supplementary for confirming bases in these participants according their benefits and therapies undertaken and these prognosic damageable tumors. LDH, noted as a biomarker of malignant tumor hypoxia and metabolic change, was markedly elevated among patients with KRAS mutation and these patients had shorter survival outcomes. Increased LDH has previously been reported to correlate to aggressive tumor phenotypes, advanced angiogenesis, and a chemotherapeutic resistant thus his supporting‹s as an prognostic indicator in lung adenocarcinoma[18].

CEA and CYFRA 21-1 levels showed a substantial decrease after starting targeted therapy and this decline matched with radiological tumor shrinkage. These markers have been widely accepted as surrogate markers of the tumor load, especially in advanced stages of adenocarcinoma. Increased CYFRA 21-1 concentration has been associated with epithelial-to-mesenchymal transition (EMT), which is a process associated with tumor growth and spread. In agreement with what has been noted, patients with solid and micropapillary variants had higher baseline CYFRA 21-1 levels and worse treatment outcomes.

These findings may explain why NSE levels were markedly higher among patients with more aggressive adenocarcinoma subtypes, especially those with features of neuroendocrine differentiation. This corresponds to earlier studies that showed NSE may act as a marker for aggressive tumor changes and for transformation to small cell lung cancer, which has an extremely unfavourable prognosis.

Incorporating NSE monitoring within the clinical framework can assist in earlier detection of histological transformation and treatment changes, thereby improving overall patient prognosis. The survival analysis further proved the existence of important disparities in PFS and OS within molecular subgroups. Patients with EGFR and ALK mutations had the best results after TKI therapy, which aligns with previous literature about the positive impact of EGFR inhibitors (osimertinib, erlotinib) and ALK inhibitors (alectinib, brigatinib) on survival[22]. On the other hand, KRAS-mutant adenocarcinomas had poorer survival and seemed to be doing so because of the strong association with high LDH, high glycolytic, and low response to traditional treatments. The

recent discovery of sotorasib and adagrasib KRAS inhibitors offer a valuable treatment option for these patients[23]. A major strength of this study lies in the full combination of histopathological, molecular and biochemical analysis to create a single model capturing all elements of lung adenocarcinoma. Nonetheless, the moderate sample size and single center scope are also caveats that might influence the scope of the results. Further research would need to be done on broad, multi-center populations and test the salt of longitudinal ctDNA monitoring as a predictor for resistance mechanism. Our conclusions strengthen the approach towards histopathological evidence combined with disease molecular characteristics and biochemistry to improve the lung adenocarcinoma patient management system.

The ability to identify biochemical markers as predictors of therapeutic response shifts the focus towards monitoring treatment dynamically, which emerges as precision oncology that seeks to hyper optimize survival while avoiding unnecessary treatment toxicity.

Conclusion

This study recognizes the need and relevance of histopathological subtyping and biochemical marker evaluation in prognosis and targeted therapy optimization with lung adenocarcinoma**. High LDH, CEA, CYFRA 21-1, and ctDNA levels associated with tumor burden and treatment resistance proved useful as prognostic biomarkers. The change of decrease in ctDNA post treatment with better survival clearly positions ctDNA as a biomarker for real time disease monitoring. Future studies need to tackle the combination of liquid biopsy with molecular and histology in order to formulate effective precision medicine approaches to improve lung cancer outcomes.

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