Use of Immunotherapy in Lung Adenocarcinoma

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Introduction:
Cancer is a group of diseases that is characterized by the uncontrollable abnormal cell growth and spreading. It can develop to harm the healthy tissues and organs within the body. The immune system is the body's mechanism to fighting off foreign bodies such as diseases, tissues, cells, etc. Immune system is supposed to recognize the abnormalities that are arising where the checkpoints are inhibiting growth and be able to destroy the cells before it grows uncontrollably. Cancer avoids these mechanisms by its ability to constantly mutate and evolve and also pass through checkpoints. Immunotherapy is a cancer treatment that allows the immune system to recognize and attack cancer cells. Immunotherapy is an attractive option to overcome cancer immune evasion because it targets crucial methods that tumors employ, which allows the root cause to stop.

Overview:
Lung cancer, specifically lung adenocarcinoma, is the most common cause of cancer death, but there is still a lot unknown about it. Lung adenocarcinoma is the most common type of lung cancer, but there is still not much known about it due to its heterogeneous nature. Originally, it was thought that smoking was the main cause of lung adenocarcinoma but as smoking rates decrease, there is starting to be a higher proportion of lung adenocarcinoma in those who do not smoke. Smoking is a clear risk factor, but up to 25% percent of people who do not smoke still end up with lung adenocarcinoma, especially in women. The main reason for this is due to gene alterations which are necessary for the process of oncogenesis. Somatic genetic alterations, which are errors acquired when incorrectly copying DNA, leads to carcinogenesis. Exposure to carcinogens from smoking, the environment, or the workplace can lead to cancer but recent studies also suggest that it comes from genetic or morphological changes in the epithelial cells in the lungs. Essentially, there are genetic alterations that can change the structure of normal functioning epithelial cells, which directly causes its functions to become altered. When looking at the clinicopathological characteristics, there is an emphasis on the driver mutations: EGFR, KRAS, and BRAF which provide insight into the cancer's progression. Everyone can become affected by lung adenocarcinoma, but in females there is a higher frequency of a specific mutation: EGFR mutation. On the other hand, the RBM10 mutation had a high prevalence in males. Overall, there is a higher risk if an individual is introduced to carcinogens(smoking, environment, workplace), but some studies suggest that while smoking is a risk, it is not the cause. Many cases of lung adenocarcinoma root from genetic or epigenetic alterations. When studying lung adenocarcinoma, there is a high presence of the mutation EGFR or Epidermal growth factor receptor, which aids in gene regulation. Mutated EGFR have dramatic responses to tyrosine kinase inhibitors. EGFR and tyrosine kinase work together to control cell proliferation. Since that function is disrupted with a mutation, cells will continue to divide which can cause cancer. New advancements in CT imaging have increased in the ability to detect pre-invasive nodules which could develop into the more harmful lung adenocarcinoma. Driver mutations such as EGFR are very important in understanding the pre-invasive stages of lung adenocarcinoma. When the pre-invasive disease is detected and surgically removed, the survival rate of the patient is close to 100%. There has been an increase in molecular targeted therapies for patients that have an identifiable driver oncogene(such as EGFR), but for most cases,

conventional chemotherapies are being used due to the lack of information on that individual's specific somatic activated oncogene. There is the presence of tumor suppressor gene abnormalities that lead to mutations, but due to the limitation in clinical advancements, there is not much known about that. Overall there is a lot to be studied about lung adenocarcinoma, and its research is extremely important in the modern world.

Cancer can evade the immune system by altering its phenotype via a process known as adaptive immune resistance. Cancer takes control of essential mechanisms designed to reduce inflammation and create immune responses (Ribas 2015). Lung adenocarcinoma has a variety of different sized epithelial cells. The transformation of epithelial cells could be a huge factor in the occurrence of lung adenocarcinoma. The main issue is the cells losing control of cell size and nucleus to cytoplasmic ratio, which are indicators of cancer(Sandlin et al. 2022). Driver mutations such as *EGFR and KRAS* are key factors in invasive lung adenocarcinoma cancer(Succony 2021). The mutation EGFR is a large focus in lung adenocarcinoma immunotherapy. Immunotherapy for certain cancers and methods is focusing on immune checkpoint inhibitors which regulate the interactions of T cells and antigen presenting cells are designed to control the driver mutations such as EGFR. EGFR is considered to be a factor in the initiation and progression of adenocarcinoma. EGFR aids in the progression of preinvasive lesions such as atypical adenomatous hyperplasia and adenocarcinoma in situ which are both similar to lung adenocarcinoma on a molecular level. EGFR mutations work with EGFR amplification, so when looking at EGFR-mutated adenocarcinoma, there is a high likelihood that EGFR amplification is a part of that. This is important because EGFR amplification plays an important role in invasive adenocarcinoma. The EGFR mutations and amplifications are essential for tumor growth and stability. In many cases, when immunotherapies and targeted therapies are directed towards the EGFR mutation in EGFR-mutated lung adenocarcinoma, it is very effective showing that EGFR has a crucial and big role in the stability and development of lung adenocarcinoma(Inamura 2018). Chemotherapy is one of the immunotherapies that can be used especially in stage 3 and 4 of lung adenocarcinoma. While there has been a significant long-term improvement in survival, the median survival period is only around 9 months. This is because chemotherapy can't target specific cells, meaning it will harm the body's normal, healthy cells. They found that many patients with this cancer have high response rates from tyrosine kinase inhibitors which is due to EGFR mutations(Jingsi 2019). In 2015, the FDA approved ICB nivolumab, an immunotherapy that targets an immune checkpoint(specifically anti-PD 1 receptor) to control advanced cancers(Rendon 2022). When observing the effects of immunotherapies, it's important that the therapies involve the targeting of EGFR alongside other common gene mutations like KRAS, HER2, ALK, ROS1, MET, BRAF, RET, and NTRK. EGFR is the most extensively studied driver mutation. Many immunotherapies are present to target EGFR such as Afatinib. Afatinib is approved by the FDA for certain kinds of EGFR mutations. Since EGFR can be manifested in several kinds of epithelial cells, there is a drug known as Cetuximab(which is FDA approved), which specifically targets the EGFR mutation in the head and neck areas. After the FDA approved the use of ICB nivolumab, several new immunotherapies have emerged with several different tactics on how to battle the ongoing case of fighting lung adenocarcinoma with immunotherapy(Jingsi 2019). There is more to learn about immunotherapies and treating lung adenocarcinoma everyday.

Review Papers

Bethune G, Bethune D, Ridgway N, Xu Z. Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update. J Thorac Dis. 2010 Mar;2(1):48-51. PMID: 22263017; PMCID: PMC3256436.

In many cases, lung adenocarcinoma can be caused by mutations in the EGFR, due to its significant response to tyrosine kinase. In general, nearly a quarter of non-small cell lung cancer(NSCLC) had mutations regarding EGFR and tyrosine kinase. When observing methods for targeted therapies, there is an emphasis on the fact that lung adenocarcinomas with mutated EGFR has significant response to gefitinib and erlotinib(which are both inhibitors of the tyrosine kinase domain of EGFR). There are still ongoing efforts to develop methods that can reliably detect abnormal EGFR, which can guide targeted therapies.

Zhang, P., Wang, W., Liu, L. et al. Analysis of prognostic model based on immunotherapy related genes in lung adenocarcinoma. Sci Rep 12, 22077 (2022). https://doi.org/10.1038/s41598-022-26427-0

The study aims to provide appropriate treatment and study patient prognosis through the use of immunotherapy. The patients are divided into high-risk and low-risk scores with various, extensive testing methods carried out. Risk score proved to be an independent factor for the progression of cancer and overall survival. The overall understanding is that patients that have higher risk-scores had a worse development of the disease. This is backed up by the study exploring differences involving the tumor immune microenvironment, immunotherapy, immune checkpoints, and tumor mutation load.

Conclusion:
Lung adenocarcinoma is a non-small cell lung cancer and the most primary lung cancer that is caused by a variety of factors. It’s shown to be treated well by immunotherapy with some patients experiencing dramatic improvements in the quality of their well-being, especially when other treatments like chemotherapy or targeted therapy are ineffective. This disease can display high levels of programmed death-ligand 1 which is a protein that can suppress the immune system's ability to attack cancer. Immunotherapy drugs can work to block these pathways and allow the immune system to better identify and target cancer cells more effectively. Some common immunotherapies used to treat lung adenocarcinoma are immune checkpoint inhibitors, cytokine targeted therapy, adoptive cell therapy, and more. The effectiveness of immune checkpoint inhibitors is based on factors like the amount of the expression that the protein programmed death-ligand 1 is exhibiting and the severity of the tumor mutation. The effectiveness of cytokine targeted therapy and adoptive cell therapy both depend on stimulating immune cell activity so it depends on mutation development. Professionals in the field are struggling with tumor heterogeneity meaning tumors have a different molecular profile and therefore different responses to immunotherapy. Another challenge is that cancer cells are constantly mutating and become resistant to these treatments. For the future of immunotherapy with lung adenocarcinoma, there will be an increase in more personalized treatment options delving into the issues of tumor heterogeneity and the rapid mutation that cancer cells exhibit. Overall, with all the notable research being made in understanding lung adenocarcinoma, there are constantly new discoveries being made that further improve the outcomes for patients who endure this disease