Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 7
MISBP 2024

Advancements in NSCLC Treatment: Efficacy and Mechanisms of Surgery, Targeted Therapy, and Immunotherapy

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Abstract. Lung cancer, the most lethal cancer form across the globe, accounts for nearly 1.8 million death each year. The high mortality rate from lung cancer underscores the critical need for effective treatments even in the face of medical progress. Currently available treatment options include radiation therapy, chemotherapy, immunotherapy, targeted therapy, and surgery. This study examines the workings and efficaciousness of the last three treatment in NSCLC. The most effective treatment for early-stage NSCLC continues to be surgical resection, offering high cure rates, especially with procedures like lobectomy and VATS. Targeted therapies have revolutionized treatment by focusing on specific genetic mutations, such as EGFR and ALK. The usage of medications like osimertinib and alectinib has achieved great success. Immunotherapy, which uses immune checkpoint inhibitors like pembrolizumab and nivolumab, has improved the immune system's ability to target cancer cells, opening up new possibilities for long-lasting responses in advanced non-small-cell lung cancer. Notwithstanding these developments, problems including immunological-related side effects and medication resistance still exist. The present status of these medicines, their modes of action, and their effects on patient outcomes are highlighted in this paper.

Keywords: lung cancer; surgery; targeted therapy; immunotherapy.

1. Introduction

Lung cancer is the most prevalent form of cancer-related fatalities worldwide, taking the lives of over 1.8 million people annually, or roughly twice the population of Delaware. This disease can take many different forms, but the most prevalent one is non-small cell lung cancer (NSCLC), which makes up around 85% of all cases of lung cancer. Large cell carcinoma, squamous cell carcinoma, and adenocarcinoma are the three main clinical classifications of non-small cell lung cancer. Hemoptysis (coughing up blood), shortness of breath, chest pain, and a prolonged cough are typical symptoms. Since the prognosis substantially worsens with advanced stages of the disease, early detection and precise diagnosis are critical.

Despite advances in treatment, the 5-year survival rate for lung cancer remains poor, underscoring the urgent need for improved therapeutic strategies and early detection methods. The genetic complexity of lung cancer makes treatment especially difficult since patients are more likely to become resistant to treatments. Common therapies include immunotherapy, targeted therapy, radiation therapy, chemotherapy, and surgery. For treatment of lung cancer in early-stage, surgery is typically the first choice; for more advanced stages, radiation therapy and chemotherapy are the main options. Despite these treatments, recurrence and tumor progression remain significant concerns. Targeted therapies have revolutionized lung cancer treatment by focusing on key genetic mutations. Lung cancer, for example, can occur as a result of mutations in the epidermal growth factor receptor (EGFR) gene, which can cause unchecked cell proliferation and division. Targeted drugs, such as gefitinib and erlotinib, inhibit the tyrosine kinase activity of the EGFR, thereby impeding tumor growth. Anaplastic lymphoma kinase (ALK) gene rearrangements can also cause aberrant signaling pathways that advance malignancy. Patients with these genetic changes have responded remarkably well to treatment with ALK inhibitors such as crizotinib and alectinib. However, the need for second- and third-generation medications arises from resistance to these treatments. Immunotherapy, which activates the host immune system to fight cancer, has emerged as another promising treatment.

Immune checkpoint inhibitors, including nivolumab and pembrolizumab, function by preventing cancer cells from using proteins like CTLA-4 and PD-1/PD-L1 to elude immune recognition [1]. As shown in the clinical test, Patients with advanced NSCLC have better survival chances as the application of immune checkpoint inhibitor could rescue the immune cell from dormant state . Because of the great degree of disease unpredictability, the cure rate is still restricted even with ongoing updates and advancements. Consequently, broad-spectrum therapeutic methods and individualized therapy are crucial. This article examines some of the most successful modern therapies, emphasizing immunotherapy, targeted therapy, and surgery.

2. Treatment Modalities for Lung Cancer

2.1. Surgery

The mainstay of treatment for NSCLC in its early stages, mostly in Stages I and II, is surgical resection. To reduce the risk of recurrence, the procedure is to remove the tumor entirely and leave a margin around any healthy tissue. Lobectomy, pneumonectomy, and minimally invasive methods like video-assisted thoracoscopic surgery (VATS) are the primary surgical treatments. For those with early-stage lung cancer, surgery provides the best chance of recovery. For example, a 5-year survival rate ranging from 60% to 80% for Stage I NSCLC has been reported after lobectomy, which entails removing the entire lung lobe [2]. VATS and other minimally invasive procedures have improved patient outcomes even more by decreasing surgical discomfort, perioperative mortality, and lengthening hospital stays. Compared to open procedures, these methods have been linked to a quicker recovery and return to regular activities [3]. Despite being extremely beneficial for those with early-stage lung cancer, surgery is typically not a reasonable option for those stepping to later stage (Stage III and IV) due to the extent of disease dissemination [4]. Moreover, there are intrinsic dangers associated with surgery, including bleeding, infection, and anesthesia-related problems. Greater risks and potential complications, such as respiratory problems and a reduced quality of life, are linked to more involved surgeries like pneumonectomy, which entails the removal of a complete lung [2]. Even when surgery is successful in treating early-stage lung cancer, recurrence of the disease may occur, requiring continued surveillance and maybe other therapies [3].

2.2. Targeted Therapy

Targeted therapies have transformed the landscape of lung cancer treatment by focusing on specific genetic mutations that drive cancer growth. Two of the most critical mutations are in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) genes.

2.2.1. EGFR Mutations

NSCLC is largely caused by unchecked cell proliferation resulting from mutations in the epidermal growth factor receptor (EGFR) gene. EGFR is a transmembrane protein that dimerizes and autophosphorylates its intracellular tyrosine kinase domain when it binds to its particular ligands, such as epidermal growth factor (EGF) or transforming growth factor-alpha (TGF-α). Multiple downstream signaling pathways, such as the PI3K-AKT, JAK-STAT, and RAS-RAF-MEK-ERK (MAPK) pathways, are triggered by this activation. Together, these pathways support angiogenesis, migration, survival, and proliferation of cells [5].

Tyrosine kinase activity of EGFR is targeted by EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, and osimertinib. TKIs stop tumor growth by the dephosphorylation of the receptor and the subsequent activation of downstream pathways. Clinical trials have shown that, in comparison to earlier-generation TKIs, osimertinib, a third-generation TKI, considerably improves both overall survival and progression-free survival (PFS). For instance, in the FLAURA study, osimertinib extended median PFS to 18.9 months compared to 10.2 months with standard EGFR TKIs [6]. Furthermore, osimertinib has superior central nervous system (CNS) penetration, making it effective against brain metastases, which are common in advanced NSCLC [7]. The understanding and

targeting of EGFR mutations continue to evolve, offering hope for more effective and tailored lung cancer therapies.

2.2.2. ALK Rearrangements

Rearrangements in the anaplastic lymphoma kinase (ALK) gene result in the production of an abnormal ALK protein that promotes cancer cell growth and proliferation. ALK is a receptor tyrosine kinase involved in normal cellular communication and signaling pathways crucial for cell development and function. When ALK is rearranged, it forms oncogenic fusion proteins, such as EML4-ALK, that lead to continuous activation of downstream signaling pathways, including the PI3K-AKT, RAS-RAF-MEK-ERK, and JAK-STAT pathways. These activated pathways promote cell proliferation, survival, and metastasis [8].

ALK inhibitors like crizotinib, alectinib, and lorlatinib have been highly effective in treating ALK-positive non-small cell lung cancer (NSCLC). Crizotinib was the first ALK inhibitor approved and showed significant efficacy in inhibiting ALK-driven tumors. However, alectinib has shown superior central nervous system (CNS) penetration and longer progression-free survival (PFS) compared to crizotinib, making it the preferred first-line treatment for ALK-positive patients. Alectinib's ability to cross the blood-brain barrier effectively targets brain metastases, which are common in ALK-positive NSCLC. Lorlatinib, a third-generation ALK inhibitor, has been developed to overcome resistance to earlier-generation ALK inhibitors and has shown promise in treating patients who have developed resistance to crizotinib and alectinib [9].

Gene therapy, particularly employing CRISPR-Cas9 technology, offers promising advancements in treating EGFR and ALK mutations in lung cancer, such as the specific ALK L1196M mutation, a single point mutation occurs at position 1196 in the ALK protein, where Leucine (CTG) is replaced by methionine (ATG) due to a single nucleotide change in the DNA sequence. This method involves using a guide RNA (gRNA) to guide the Cas9 enzyme to the target position where it makes precise cuts, allowing for the introduction of a correct sequence during the repair process [Fig.1]. CRISPR-Cas9 can directly modify or correct these mutations at the genetic level, potentially halting cancer progression. Early studies have shown its ability to target and alter these specific mutations effectively, paving the way for personalized therapeutic approaches. However, challenges such as off-target effects, where Cas9 may bind and cut at unintended sites, and the complexities of delivery methods, remain significant. The predominant repair pathway in mammalian cells, non-homologous end joining (NHEJ), is more error-prone and can lead to new mutations, adding another layer of complexity. Long-term safety and ethical concerns surrounding gene editing in humans also need careful consideration and ongoing research to enhance the technology's safety and effectiveness.

Targeted therapies offer a high degree of specificity, attacking only the cancer cells, which shows little side effects compared to traditional chemotherapy. Additionally, many targeted therapies are available in oral formulations, enhancing patient convenience and adherence to treatment [3]. These therapies have shown significant efficacy in advanced and metastatic NSCLC, especially in patients with brain metastases, where traditional treatments are less effective. However, the primary challenge with targeted therapies is developing resistance. Cancer cells can develop secondary mutations or activate alternative signaling pathways, diminishing the effectiveness of initial treatments. This has led to the development of next-generation inhibitors to avoid resistance. Furthermore, targeted therapies are only beneficial for patients with specific genetic mutations, limiting their applicability across the broader lung cancer patient population.

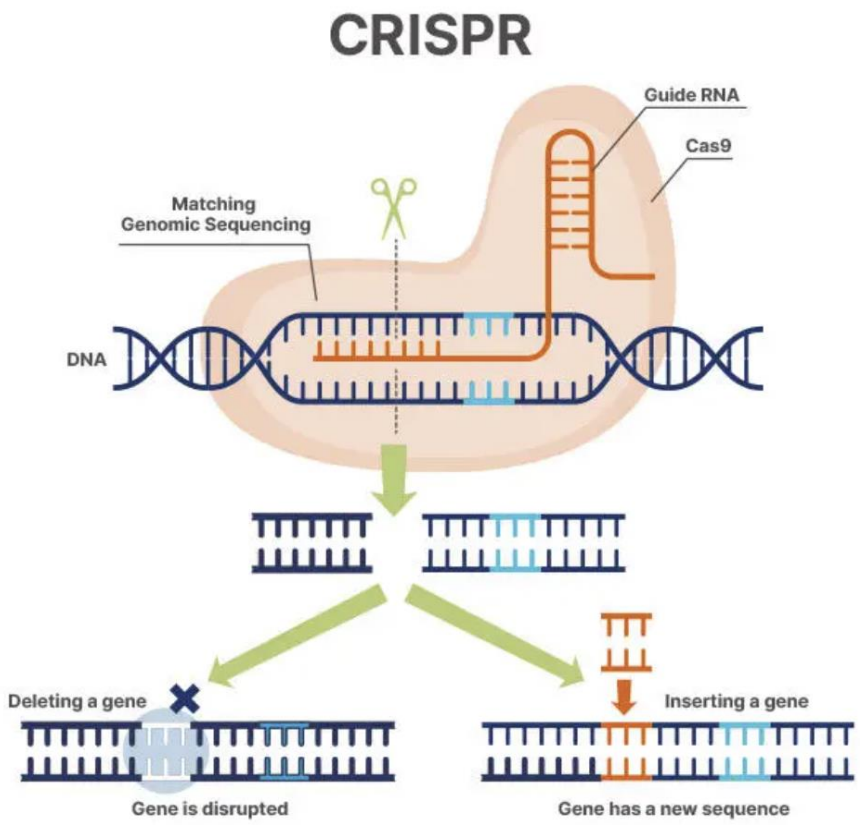

Figure 1. Mechanism of CRISPR-Cas9

2.3. Immunotherapy

By boosting the body's immune response against the cancer, immunotherapy is a major improvement in the treatment of advancedNSCLC. Pembrolizumab and nivolumab, two immune checkpoint inhibitors, particularly target proteins like CTLA-4 and PD-1/PD-L1, which are essential for immune control. Immune checkpoints are essential in normal conditions for preserving self-tolerance and controlling the immune response to avoid autoimmunity by giving T-cells the required inhibitory signals. These checkpoints, however, can be used by cancer cells to avoid immune detection. For instance, cancer cells that express PD-L1 can bind to T-cell PD-1 receptors, so "turning off" these immune cells and preventing their destruction [10].

Another promising immunotherapy approach is Chimeric Antigen Receptor T-cell (CAR-T) therapy. CAR-T therapy involves engineering a patient’s T-cells to express a receptor that specifically targets tumor-associated antigens. Once these modified T-cells are infused back into the patient, they can recognize and attack cancer cells more effectively. Although CAR-T therapy has shown remarkable success in hematologic malignancies, its application in solid tumors like NSCLC is still under investigation due to challenges like the tumor microenvironment and antigen heterogeneity. Early clinical trials are exploring the potential of CAR-T cells targeting specific antigens present in lung cancer, showing encouraging preliminary results and paving the way for future advancements in this field [11].

2.3.1. Mechanism of Action

These drugs work by enhancing the immune system's ability to recognize and destroy cancer cells. Clinical studies have demonstrated that immunotherapy can lead to durable responses and significant improvements in overall survival for patients with advanced NSCLC. The interaction between PD-1 on T-cells and PD-L1 on tumor cells is a primary target of some immunotherapies, which block PD-1 or PD-L1, enhancing the body’s immune response against the tumor. CTLA-4 is another checkpoint targeted by immunotherapies like ipilimumab, which functions earlier in the immune response than PD-1 by affecting T-cell activation in lymph nodes.

2.3.2. Benefits and Challenges

One of the most notable benefits of immunotherapy is its potential to produce long-lasting responses, even in cases where traditional treatments have failed. When combined with chemotherapy, immunotherapy has shown enhanced efficacy, becoming a standard first-line treatment for metastatic NSCLC. Moreover, unlike targeted therapies, immunotherapy can be applied broadly across various patients without the need for specific genetic mutations. However, despite its benefits, immunotherapy is associated with immune-related adverse effects, as the activation of the immune system can sometimes lead to inflammation of healthy tissues. Common side effects include pneumonitis, colitis, and hepatitis, which require careful management and monitoring [2]. Additionally, not all patients respond to immunotherapy, and predictive biomarkers to identify responders are still under investigation. The high cost of immunotherapy also poses a financial challenge for patients and healthcare systems.

2.3.3. Similarities and Differences Between PD-1/PD-L1 and CTLA-4

While PD-1 and CTLA-4 are both immune checkpoints, they operate at different phases of the immune response. CTLA-4 works in the early stage of T-cell activation. By disrupting the interaction between the stimulatory receptor CD28 and B7 molecules on antigen-presenting cells, the naive T cells remain in the quiescent state. In contrast, PD-1 primarily regulates immune responses in the peripheral tissues during the later stages of T-cell activation. Blocking CTLA-4 can lead to a broader activation of the immune system compared to targeting PD-1/PD-L1, which is more focused on enhancing the activity of T-cells specifically within tumors. This distinction is crucial for understanding their therapeutic effects and side effect profiles, which can guide the choice of immunotherapy in clinical practice [12].

3. Summary

The advancements in lung cancer treatment through surgery, targeted therapy, and immunotherapy have significantly improved patient outcomes, particularly for those with NSCLC. Surgical resection remains the best option for early-stage disease, providing high cure rates. Targeted therapies have revolutionized the treatment of genetically defined subsets of lung cancer, though resistance remains a significant challenge. Immunotherapy has introduced new possibilities for long-term control of advanced NSCLC, with the potential for durable responses. As personalized medicine continues to evolve, tailoring treatments based on individual genetic profiles and integrating these modalities will be crucial for optimizing efficacy and improving survival rates in lung cancer patients. Continuous research and clinical trials are essential to address the existing challenges and develop new therapeutic strategies, offering hope for better outcomes in the future.

References

[1] J.R. Brahmer, S.S. Tykodi, L.Q. Chow, W.J. Hwu, S.L. Topalian, P. Hwu, ... J.D. Powderly, Safety and activity of anti-PD-L1 antibody in patients with advanced cancer, New England Journal of Medicine. 366 (2012) 2455-2465. doi:10.1056/NEJMoa1200694.

[2] American Cancer Society. (2020). Cancer facts & figures 2020. Information on https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html

[3] National Cancer Institute. (n.d.). Lung cancer—patient version. Information on https://www.cancer.gov/types/lung

[4] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2020, CA: A Cancer Journal for Clinicians. 70 (2020) 7-30. doi:10.3322/caac.21590.

[5] N. Normanno, C. De Luca, A. Maiello, S. Campiglio, S. Napolitano, S. Mancino, G. Carotenuto, M. Agrawal, A. Halmos, L. Rosell, Epidermal growth factor receptor (EGFR) signaling in cancer, Gene. 366 (2006) 2-16.

[6] J.C. Soria, G.J. Kim, J.J. Wu, Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer, New England Journal of Medicine. 378 (2018) 113-125.

[7] T. Reungwetwattana, T.S. Mok, L. Spigel, Central nervous system response to osimertinib in patients with T790M-positive advanced non-small-cell lung cancer: pooled data from two Phase II studies, Journal of Clinical Oncology. 36 (2018) 1542-1550.

[8] B. Hallberg, R.H. Palmer, Mechanistic insight into ALK receptor tyrosine kinase in human cancer biology, Nature Reviews Cancer. 13 (2013) 685-700.

[9] J.C. Soria, H. Tan, E. Chiari, Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer, New England Journal of Medicine. 377 (2017) 829-838.

[10] J. Zhao, Q. Lin, Y. Song, D. Liu, Universal CARs, universal T cells, and universal CAR T cells, Journal of Hematology & Oncology. 12 (2019) 1-9.

[11] K. Newick, S. O'Brien, E. Moon, S.M. Albelda, CAR T cell therapy for solid tumors, Annual Review of Medicine. 68 (2017) 139-152.

[12] S.V. Sharma, D.W. Bell, J. Settleman, D.A. Haber, Epidermal growth factor receptor mutations in lung cancer, Nature Reviews Cancer. 7 (2007) 169-181. doi:10.1038/nrc2088.

[13] Revolutionizing Gene Editing with CRISPR Cas9, information on https://lifesciences.danaher.com/us/en/library/crispr-cas9.html