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Small molecule compounds and monoclonal antibody therapy in lung cancer

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Abstract. The leading cause of cancer-related mortality worldwide is lung cancer, with ongoing challenges in treatment efficacy and safety, but recent advances have been made in targeted therapies, including small molecule inhibitors and monoclonal antibodies, have significantly improved treatment precision and reduced side effects compared to traditional methods. Despite these developments, gaps remain in fully understanding resistance mechanisms and identifying novel therapeutic targets. This paper reviews the current state of targeted therapies for lung cancer, examining their mechanisms, clinical applications, and impact on patient outcomes. It provides valuable insights into how these therapies have advanced the field and highlights areas where further research is needed. Future studies should focus on addressing these gaps and exploring new approaches to optimize treatment and enhance patient survival rates.

Keywords: Lung cancer, risk factors, immunotherapy.

1. Introduction

Despite ongoing medical advances, LC (LC) is still one of the malignant tumors that threaten people's health worldwide [1]. Cancer remains a significant global health issue, with various types of challenges in prevention and treatment. Among the many methods contributing to cancer treatments, the targeted therapies have gained considerable attention. In recent years, extensive research has been conducted to identify the use of targeted therapy methods like small molecule compounds and monoclonal antibody treatment to treat LC.

The LC remains necessitating continual advancements in treatment strategies to improve patient outcomes. The development of targeted medicines in recent decades has completely changed the way LC is managed, providing more individualized and efficient treatment plans. The goal of targeted therapy is to obstruct particular molecular changes that help cancer cells grow and survive, thereby exerting therapeutic effects while sparing healthy tissues. Among these targeted approaches, small molecule compounds and mAbs have emerged as pivotal agents in the therapeutic armamentarium against LC. Specific molecular targets associated with cancer or other diseases are the focus of targeted therapy as a treatment approach [2]. Its goal is to interfere with disease progression precisely, minimizing damage to normal cells [2]. mAb therapy is a form of targeted therapy that uses laboratory-made antibodies designed to attach to specific antigens found on cancer cells, stopping their growth or marking them for destruction by the immune system [3]. Small molecule compounds, on the other hand, target specific intracellular enzymes or signaling pathways to disrupt cancer cell growth and proliferation [4].

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Currently, targeted therapies are widely used in treating various cancers. For instance, mAbs like trastuzumab (Herceptin) are used for HER2-positive breast cancer (BC), while small molecule inhibitors like imatinib (Gleevec) target specific kinases in chronic myeloid leukemia (CML).

Both small molecule and monoclonal antibody therapies have significant potential. The prospect for small molecule therapies lies in their ability to penetrate cells and target internal processes, offering a wide range of applications. Monoclonal antibody therapies are promising, their specificity and ability to activate the immune system can lead to more effective and less toxic treatments. The development and application of these therapies continue to advance, offering hope for more personalized and effective treatment options. Traditional approaches such as chemotherapy and radiation therapy have provided limited success, often accompanied by significant adverse effects. Both malignant and healthy cells are generally impacted by radiation and chemotherapy [5]. Targeted therapies hold out the possibility of more potent and less hazardous treatment options by attempting to specifically interfere with the molecular pathways essential for cancer cell survival [5]. Thus, targeted therapies utilizing small molecule compounds and mAbs have emerged as promising alternatives [6]. The paper explores the mechanisms and principles of epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and mesenchymal-epithelial transition (MET) of targeted therapies in LC, for instance, focusing on the development, mechanism of action, clinical significance, application status, side effects and safety evaluation of small molecule compounds and mAbs [7-9].

By elucidating these advancements, the author aims to underscore their potential in the landscape of LC treatment and improve patients' survival rates. This paper will analyze the treatment of LC from the perspective of targeted drugs. Based on the analysis, suggestions will be put forward for the development of future targeted drugs, and suggestions for optimization of future research and development of targeted drugs.

2. Risk factors

2.1. Smoking

Smoking is the most significant risk factor for lung cancer, with extensive evidence linking it to increased incidence rates. Carcinogens present in tobacco smoke, such as benzene, formaldehyde, and polonium-210, damage DNA in lung cells, initiating mutations that can lead to cancer [10]. According to an extensive study conducted by the International Agency for Research on Cancer (IARC), smoking is the primary cause of lung cancer in about 85% of cases [10]. Additionally, smoking induces inflammation and impairs the immune system, further increasing the risk of cancer development [10].

2.2. Environmental and occupational exposures

Exposure to environmental and occupational carcinogens is another major risk factor for LC. Research highlights the dangers of asbestos, radon, and certain industrial chemicals. Asbestos Exposure: Asbestos fibers can cause lung damage and mutations leading to LC. The U.S. Environmental Protection Agency (EPA) and the American Cancer Society report that asbestos exposure significantly increases the risk of lung cancer, particularly among workers in industries such as construction and shipbuilding [10]. Radon exposure also play an important role. Radon, a naturally occurring radioactive gas, is linked to LC risk. The National Cancer Institute (NCI) states that, after smoking, lung cancer caused by the second most common factor in the US [10]. Past study that radon exposure accounts for about 21,000 lung cancer deaths annually in the U.S. [10]. Exposure to certain industrial chemicals, such as arsenic and diesel exhaust, has been linked to a higher risk of cancer. For example, Diesel engine exhaust is classified as a Group 1 carcinogen according to research conducted by the International Agency for Research on Cancer (IARC), highlighting its role in increasing lung cancer risk [10].

2.3. Genetic predispositions

Genetic factors also contribute to LC risk. Specific genetic mutations and hereditary factors can increase susceptibility. For instance, BRCA1 and BRCA2 Mutations. While primarily associated with breast and

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ovarian cancers, these mutations can also influence lung cancer risk. A study found that individuals with BRCA2 mutations have an elevated risk of developing LC, although this association is less well-established compared to other cancers [11]. Air pollution exposure for an extended period of time is a major risk factor for LC. Studies have shown that pollutants such as particulate matter (PM2.5) and nitrogen dioxide (NO_2) contribute to increased cancer risk. The research indicates that long-term exposure to high levels of air pollution is associated with a higher incidence of LC, particularly in urban areas with high traffic pollution [10].

2.4. Air pollution

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2.5. Lung diseases

Chronic lung diseases, including chronic obstructive pulmonary disease (COPD) and tuberculosis, increase the risk of LC. These conditions involve persistent inflammation and lung damage. The relationship between COPD and LC is well-documented. A study found that patients with COPD have a significantly higher risk of developing LC compared to non-mokers [10]. Individuals with a history of tuberculosis also face an increased risk of LC due to chronic lung inflammation and scarring. The research highlights that tuberculosis survivors have a heightened risk of LC, especially if they were smokers [10].

2.6. Age and gender

Age and gender influence LC risk, often linked to smoking patterns and genetic factors. Older individuals are more susceptible due to the accumulation of genetic mutations and a declining immune response. the research shows that the risk of LC increases with age, with a notable increase after age 50 [12]. Gender differences in LC risk are often related to historical smoking patterns, with males historically having higher rates of smoking and LC compared to females [10].

2.7. Nutritional deficiencies

Poor dietary habits and nutritional deficiencies can affect LC risk. Nutritional deficiencies impair the body's ability to repair DNA and maintain immune function. Studies, such as papers published have found associations between low levels of vitamins A, C, D, and folate and an increased risk of LC due to their roles in cellular repair and immune response [11].

2.8. Prior radiation treatment

Radiation therapy for other cancers can increase LC risk. Radiation-induced lung cancer is particularly associated with high doses and prolonged exposure. According to the research, patients who receive radiation therapy for breast cancer are at a higher risk of developing LC later in life [12].

3. Targeted therapies

Targeted therapy is a paradigm shift in cancer treatment, which is why it's important to understand its principles, concentrating on the specific molecular abnormalities that are responsible for tumor growth and progression [5]. The foundation of targeted therapy lies in its ability to exploit specific molecular aberrations present in cancer cells.

1) Genetic mutations: The function of key proteins involved in cell growth and survival is often altered by genetic mutations in cancer cells [5]. Targeted therapies can inhibit these mutated proteins or their downstream signaling pathways [5]. In CML, tyrosine kinase inhibitors (TKIs) like imatinib are employed to attack the BCR-ABL fusion protein, a result of a chromosomal translocation specific to this leukemia [5].

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2) Protein overexpression: some cancers are characterized by the overexpression of certain proteins that drive their growth [5]. MAbs, such as trastuzumab, target HER2, a receptor that is overexpressed in some BCs [5]. By binding to HER2, trastuzumab blocks it signaling, thereby inhibiting cancer cell proliferation [5].

3) Abnormal signal pathways: cancer cells frequently activate signaling pathways that promote their survival and proliferation [5]. Targeted therapies can interrupt these pathways [5]. For example, inhibitors of the mTOR pathway, such as everolimus, are used to treat tumors that exhibit aberrant mTOR signaling [5]. Targeted therapies can be categorized based on their mechanisms and the types of molecules they target [5]. For instance, mAbs are lab-engineered molecules designed to bind to specific antigens in cancer cells [5]. By targeting these antigens, The immune system can destroy cancer cells by marking them, blocking their growth signals, or delivering cytotoxic agents directly to them, mAbs can be utilized [5]. Examples include rituximab, which targets CD20 on B cells in non-Hodgkin lymphoma, and bevacizumab, which inhibits VEGF to prevent angiogenesis [5]. Small molecule inhibitor drugs are designed to enter cells and interfere with specific proteins involved in cancer growth [5]. Small molecule inhibitors can target protein kinases, such as those involved in cell signaling and proliferation [5]. For instance, gefitinib and erlotinib are EGFR inhibitors used in non-small cell LC (NSCLC) [5].

4. Therapeutic vaccines

Although cancer vaccines are less common, cancer vaccines stimulate the immune system to target and destroy cancer cells [5]. They are designed to provoke an immune response against specific tumor-associated antigens [5]. Hormone therapy is good for cancers like breast and prostate cancer, hormone therapies can block the production or action of hormones (estrogen and testosterone) that fuel cancer growth [5]. Drugs such as tamoxifen and aromatase inhibitors are used to target estrogen receptors in BC [5]. Personalized medicine and precision oncology is one of the major advancements in targeted therapy is the move toward personalized medicine tailors treatment based on the unique genetic and molecular profile of an individual's tumor [10]. This approach involves molecular profiling, identifying specific genetic mutations, protein expressions, or other molecular abnormalities in a patient's tumor, which helps in selecting the most appropriate targeted therapy [5]. Techniques such as next-generation sequencing (NGS) and proteomics are commonly used in molecular profiling [5]. Biomarker Testing are measurable indicator of the presence or progression of disease [5]. In targeted therapy, biomarker testing helps to identify patients who are most likely to benefit from specific therapies [5]. For example, testing for BRCA1 and BRCA2 mutations can help determine eligibility for PARP inhibitors in breast and ovarian cancers [5].

Targeted therapies have several significant advantages in cancer treatment, as illustrated by specific applications.

1) Reduced off-target effects: Targeted therapies are designed to specifically address molecular abnormalities found in cancer cells, thereby reducing the impact on normal cells. For instance, Herceptin (trastuzumab) targets the HER2 protein, which is overexpressed in some breast cancers. A study found that Herceptin significantly reduces the risk of cancer recurrence compared to traditional chemotherapy and causes fewer side effects [5].

2) Reduced toxicity and side effects: Targeted therapies often result in Gleevec (imatinib), a targeted therapy for chronic myeloid leukemia (CML), has fewer side effects than conventional treatments., specifically inhibits the BCR-ABL fusion protein. Research indicates that Gleevec has fewer side effects than traditional chemotherapy drugs, leading to improved patient quality of life [5].

3) Improved clinical outcomes: Targeted therapies have been shown to enhance clinical outcomes. Olaparib, a PARP inhibitor, is used for treating BRCA mutation-positive ovarian cancer. Clinical trials demonstrate that Olaparib significantly extends progression-free survival and has fewer adverse effects compared to standard treatments [5].

4) Optimized Treatment Effectiveness: Targeted therapies can improve treatment effectiveness by focusing on specific molecular targets. Alecensa (alectinib) is used for ALK-positive non-small cell lung

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cancer (NSCLC). Studies reveal that Alecensa effectively controls disease progression and has a favorable side effect profile, improving overall survival and patient quality of life [5].

Targeted therapies represent a sophisticated approach to cancer treatment by focusing on specific molecular abnormalities unique to cancer cells. They offer the potential for more effective and less toxic treatment options compared to traditional therapies. However, ongoing research is essential to address the challenges and optimize the benefits of targeted therapies in oncology [5].

5. Conclusion

This paper provides a comprehensive review of the current advancements in lung cancer treatment through targeted therapies, focusing on small molecule compounds and monoclonal antibodies. It highlights the significant progress in developing more precise treatment options compared to traditional therapies, such as chemotherapy and radiation, which have broader effects and higher toxicity. By targeting specific molecular abnormalities associated with cancer, these therapies offer improved efficacy and reduced side effects. However, the paper also acknowledges the limitations, such as incomplete understanding of resistance mechanisms and the need for more extensive research into novel targets and biomarkers. The insights provided here underscore the promise of targeted therapies and suggest that future research should concentrate on overcoming these challenges to further enhance personalized treatment approaches. This will be crucial in advancing the field and improving patient outcomes in lung cancer treatment.

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