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Research Status And Development Trend Of Monoclonal Antibodies For Non-Small Cell Lung Cancer

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Abstract. Lung cancer remains the leading cause of cancer-related mortality globally, with non-small cell lung cancer (NSCLC) accounting for 80% of cases. Traditional chemotherapy faces limitations such as non-specific cytotoxicity, transient efficacy, and resistance due to tumor heterogeneity. Monoclonal antibodies (mAbs) have emerged as transformative agents, offering targeted therapy with improved specificity and reduced toxicity. Recent advancements include immune checkpoint inhibitors anti-angiogenic agent, and innovative formats such as antibody-drug conjugates (ADCs) and bispecific antibodies. Despite progress, challenges persist in overcoming resistance mechanisms, optimizing combination therapies, and expanding biomarker-driven approaches. This article analyzes the evolution of mAbs in NSCLC treatment, focusing on their mechanisms, clinical application, and new developments. The study underscores the role of mAbs in enabling precision medicine through multi-target inhibition, synergistic combinations, and adaptive trial designs. These advancements provide a roadmap for personalized NSCLC management, yet unresolved issues include resistance to EGFR/ALK inhibitors, optimal ADC linker stability, and heterogeneity in treatment response. Future research should prioritize novel targets, integrate multi-omics for biomarker discovery, and refine immunomodulatory strategies to transform NSCLC into a chronic manageable disease.

Keywords: Non-small-cell lung cancer, monoclonal antibodies, target therapy.

1. Introduction

Lung cancer is the prime cause of cancer-related death worldwide, with the highest mortality rates in both men and women and is responsible for a large number of deaths globally. The International Agency for Research on Cancer's (IARC) presents that lung cancer remains the leading cause of cancer death, causing an estimated 1.8 million deaths (18%) in 2020. Non-small cell lung cancer (NSCLC) accounts for about 80% of all lung cancers, and about 75% of patients are already in the middle and late stages when detected, and the 5-year survival rate is very low. As a result, the development of effective therapy for NSCLC has become a crucial factor of human health. However, when using traditional chemotherapy, there are many restrictions. Its curative effect has many limitations. Chemotherapy is only effective on part of patients and the effect of it is transitory. Tumors are prone to recurrence or progression within a few months, requiring frequent replacement regimens for the reason that NSCLC is highly heterogeneous, chemotherapy is difficult to cover all clones, and some cells remain leading to recurrence. Additionally, chemotherapy lacks specificity and precision, causing great pain to patients. To solve these problems, monoclonal antibodies (mAbs) are introduced into the treatment of NSCLC, creating a brand new situation [1]. Compared to the traditional chemotherapy, mAbs have many advantages. As a result, it is a potential solution to the treatment of NSCLC, being hopeful to save millions of lives. Being aware of the situation, a lot of resource is put into the research of mAbs and great achievements has been made. Being a kind of antibody, mAbs are able to pinpoint cancer cells. It causes little pain to the patient, being one of the main reasons why people choose it as a better therapy compared with traditional chemotherapy. For now, many new therapies based on mAbs are developed. The development of combination immunotherapy, antibody drug conjugates (ADCs), and bispecific antibody has greatly enhanced the effect of mAbs in the treatment This article mainly focus on the research and the development of mAbs in order to show its effect on the treatment of NSCLC, predicting its future development.

2. The Applications of mAbs in Cancer Treatment

2.1. The Principle of mAbs

mAbs are highly uniform antibodies produced from the cloning of a single B lymphocyte, targeting only a specific epitope. Because of the high specificity and large-scale production, mAbs are of great value in medical diagnosis, treatment and basic research [2].

mAbs technology is a molecular biology technology developed by two scientists, Kohler and Milstein. mAbs technology is based on hybridoma cell technology. The function of secreting antibodies is carried out by B lymphocytes, and B lymphocytes cannot live permanently. To obtain large amounts of mAbs, Kohler and Milstein fused mouse myeloma cells (sp2/0) with mouse spleen cells that had been immunized with sheep red blood cells to form hybridoma cells by using either a pegylated fusion agent or an inactivated Sendai virus. Hybridoma cells can not only secrete antibodies against a specific antigen, but also survive forever in vitro culture like infinite tumor cells [3].

The basic principle of mAb preparation is as follows. Inject foreign substances into the animal, when the animal is stimulated by external antigens, the body can produce corresponding specific immune response through humoral immunity or cellular immunity, and the survival time of plasma cells secreting antibodies is very short and cannot exist in the animal body for a long time. When the body is again stimulated by the same antigen, the memory cells will be activated, and the activation will soon produce a large number of specific antibodies against the antigen. After repeated stimulation, a mouse's spleen would contain many of these plasma cells. The splenic cells are fused with sp2/0 cells to form hybridoma cells.

2.2. The Effect of mAbs in the Treatment

The efficacy of conventional chemotherapy and radiotherapy in treating NSCLC patients is limited for the reason that the high doses required for tumor often lead to irreversible damage to normal tissues. In human body, there are a lot of factors that are necessary for the survival of the tumor cells or will promote the growth of the tumor cells. Targeting these factors, we can develop the mAbs product that will bind to these factors. With the high doses needed and high specificity, mAb therapy not only enhances therapeutic efficacy for patients but also reduces side effects, which improves patient tolerance and compliance with treatment. Currently, there have been many approved biologics for treating NSCLC.

Taking Durvalumab as an example, according to the results of the AEGEAN 2 Interim analysis presented at the World Conference on Lung Cancer (WCLC) Annual Meeting in 2024, compared with patients in the control group (placebo combined with chemotherapy as preoperative neoadjuvant therapy and placebo as postoperative adjuvant therapy), the median event-free survival (EFS) time is significantly longer in the Durvalumab group. At the same time, perioperative use of it is associated with a 31% reduction in the risk of disease progression, recurrence, or death [4].

Moreover, another mAbs product Pembrolizumab is also effective. The median percentage of residual surviving tumors (%RVT) in the Pembrolizumab group is 29.5% (95%CI 1.0% to 56.0%) and the median %RVT is 52.0% (29.0% to 68.0%) in the placebo group. The duration of EFS in all patients is negatively correlated with %RVT. Compared with placebo, the Pembrolizumab group improved EFS values in almost every %RVT.

As a conclusion, many mAbs have been put into the treatment of NSCLC, and their therapeutic efficacy have been proved by current data to be effective.

2.3. MAb Drugs already being Used

The development of immune checkpoint inhibitors (ICIs) has greatly improved the treatment of NSCLC. Currently common immune checkpoints include programmed death protein 1 (PD‐1), programmed death ligand‐1 (PD‐L1) and Cytotoxic T lymphocyte‐associated antigen 4 (CTLA4).

Focusing on these immune checkpoints, many mAbs products have been developed. Sintilimab, Pembrolizumab and Durvalumab are all mAbs products developed based on ICIs.

Pembrolizumab is a humanized mAb that can overcome "immune escape" mediated by PD-1. By binding to PD-1 on T cells and reactivate T cells' immune surveillance of tumor cells, playing an anti-tumor role [5].

Sintilimab is an anti-PD‑1 fully human IgG4 mAbs produced in China, which can bind to the PD‑1 molecule on T cells, so it has the characteristics of high affinity, durable stability and improved target occupancy. There is evidence that Sintilimab may be more economical in China compared to Pembrolizumab.

Vascular endothelial growth factor (VEGF) promotes tumor growth because it has the function of increasing vascular permeability, extracellular matrix degeneration, vascular endothelial cell migration, proliferation, and angiogenesis. Targeting on VEGF, Bevacizumab is developed. Bevacizumab is a humanized mAb against VEGF by reducing tumor expansion by controlling abnormal vascular growth around tumors.

Additionally, Cetuximab is a recombinant human/mouse IgG1 chimeric mAb that binds to the epidermal growth factor receptor (EGFR) and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, thereby blocking the downstream signaling pathway of ligand-induced EGFR phosphorylation and apoptosis. It showed good curative effect in advanced patients. mAbs, as the core approach of targeted therapy for non-small cell lung cancer, continuously promotes the development of individualized medicine. With the discovery of new targets and the advancement of technologies such as bispecific antibodies and ADCs, the position of mAbs in cancer treatment will be further enhanced, providing patients with more efficient and low-toxicity treatment options.

3. The Current Research of mAbs

3.1. The Drawbacks of the mAbs

In the process of using mAbs, the drawbacks of mAbs are also presented. Firstly, most mAbs are against only a single target, increasing the possibility that the tumor cells will develop resistance by mutation. For example, EGFR mAbs will be resisted when mutation happens on Kirsten rats arcomaviral oncogene homolog (KRAS). Secondly, the growth of NSCLC involves multiple paths, and it is impossible for a single antibody to cover all the paths. Thirdly, for some of mAbs, the duration of the effect is short compared with chemotherapy. Additionally, the curative effect is largely influenced by the genotypes and microenvironments of the patients, causing a large individual difference.

3.2. The Applications of Combination Immunotherapy

Facing the situation that the signaling pathways related to tumor growth and proliferation are multi-pathway, combination immunotherapy is put into used. For now, the combination of radiotherapy and mAbs has been developed to improve the limited overall response rates with susceptibility to resistance of immunotherapy [6]. For example, anti-PD‑1 mAbs can only block one immunosuppressive pathway, and the tumors may evade immune attacks through other pathways. The use of radiotherapy will significantly reduce the immune escape rate of cancer cells because radiation- induced tumor cell death will release tumor- associated or tumor- specific antigens which can then be targeted by the host immune system. Moreover, the combination of mAbs and chemotherapy or other non-monoclonal antibody immunosuppressants also plays an important role in clinical practice. However, the severe side effects of radiotherapy and chemotherapy are supposed to be taken into consideration in practical treatment [7].

3.3. The Development of ADCs

Since the first batch of ADCs based on human-mouse chimerism and humanized monoclonal antibodies were developed, ADC has become one of the fastest-growing treatment approaches in the field of NSCLC treatment because of its fewer off-target effects and wider treatment window. ADC consists of three parts: mAb, cytotoxic drugs and a unique linker that connects these two.

In ADCs, mAbs are an important component. mAb mediates ADC binding to the target antigen on the target cell to exert its medicinal effect. In addition to targeting effects, the mAb components of many ADCs have active characteristics and can interact with the functions of target cells, altering downstream signal transduction [8].

Current ADC drugs have seen significant improvements in terms of specificity and cytotoxicity. In the treatment of NSCLC, ADC targeting HER2 have been proven effective. HER2 is one of the important members of the EGFR family. HER2 abnormalities are closely related to the occurrence of various malignant tumors, and most of them suggest a poor prognosis. In NSCLC, the dysregulation of HER2 signaling can be caused by mutations, amplifications and overexpressions. Trastuzumabderuxtecan is an ADC targeting HER2. The topoisomerase I inhibitor it carries can bind to DNA topoisomerase I and DNA, and form a stable tricomplex, thereby inducing DNA damage and leading to apoptosis [9].

ADC has driven a new trend in the field of individualized NSCLC treatment. At present, significant progress has been made in the research of drugs targeting HER2, which is expected to bring the next therapeutic breakthrough to patients. However, there are still some challenges, including drug resistance, safety, and efficacy.

3.4. The Development of Bispecific Antibody

For patients with advanced NSCLC who have received frontline immunochemotherapy, following treatment options are limited. PD-1/CTLA-4 bispecific antibody is one of the few answers. PD-1 and CTLA-4 play different roles in immunosuppression. PD-1 inhibits the function of T cells in the tumor microenvironment, while CTLA-4 mainly inhibits the activation of T cells in lymph nodes. Bispecific antibodies activate a more comprehensive immune response by simultaneously blocking these two pathways. When traditional PD-1 mAbs are used in combination with CTLA-4 mAbs, the problem of toxicity superposition is significant [10]. Bispecific antibodies reduce the risk of toxicity by optimizing molecular structure and dosage design. Additionally, bispecific antibodies have broken through the limitation of PD-L1 expression level on therapeutic effect, especially showing significant benefits for patients with low or negative PD-L1 expression Therefore, the development of PD1 / CTLA4 bispecific antibodies has become a choice for global pharmaceutical companies, as they have therapeutic advantages that monoclonal antibodies cannot match [11].

In an era of rapid development of biotechnology, mAb technology is facing multiple development directions including combination immunotherapy, ADCs, and bispecific antibody. Each of them deserves further study, having the potential to become an answer for the treatment of NSCLC.

4. Conclusion

This article comprehensively reviews the transformative role of mAbs in the treatment of NSCLC, emphasizing evolution of treatment method from conventional chemotherapy to precision immunotherapy. By targeting specific molecular pathways such as PD-1/PD-L1, CTLA-4, VEGF, and EGFR, mAbs like Pembrolizumab, Durvalumab, and Bevacizumab have demonstrated superior efficacy in improving EFS and reducing recurrence rates, as evidenced by clinical trials such as AEGEAN. These advancements address the limitations of traditional chemotherapy, including non-specific cytotoxicity, transient efficacy, and high heterogeneity-driven resistance. Furthermore, the development of combination therapies, ADCs, and bispecific antibodies has expanded the therapeutic

landscape, offering solutions to challenges like immune escape, multi-pathway tumorigenesis, and toxicity limitations.

The significance of these findings lies in their alignment with the urgent need for personalized, low-toxicity therapies highlighted in the introduction. By leveraging mAbs' specificity and adaptability, researchers have not only improved patient outcomes but also laid the groundwork for future innovations. For instance, ADCs such as trastuzumabderuxtecan exemplify how cytotoxic payloads can be delivered selectively to tumor cells, minimizing off-target effects. Similarly, PD-1/CTLA-4 bispecific antibodies overcome the toxicity barriers of dual checkpoint inhibition while broadening efficacy across PD-L1 expression levels. These breakthroughs underscore the potential of mAbs to redefine NSCLC treatment paradigms, particularly for advanced-stage patients. This review suggests that future research should focus on overcoming residual challenges, such as drug resistance mechanisms, optimizing ADC linker stability, and identifying novel tumor-specific targets.

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