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Research Progress on Antibody-Drug Conjugates Therapy for Non-Small Cell Lung Cancer (NSCLC)

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Abstract: Non-small cell lung cancer (NSCLC), recognized as a primary contributor to cancer-related fatalities on a global scale, makes for around 85% of all diagnosed lung cancer instances. Antibody-drug conjugates (ADC), recognized as a cutting-edge approach in cancer therapy, have demonstrated good curative effects in the treatment of numerous malignant cancers in recent years, encompassing NSCLC therapy. These drugs not only increase the patients' survival cycle and remission rate to a certain degree but also lessen harmful side effects and other side effects thanks to their precise guidance feature.They combine the potent damage impact of conventional chemotherapeutic medications with the specific target ability of monoclonal antibodies, overcoming the limitations of those conventional therapeutic approaches, including as targeted therapy, immunotherapy and so on, in terms of drug resistance and cancer progression. With the accumulation of more clinical data and optimization of technology, it gives rise to new expectations pertaining to the therapeutic approach for patients diagnosed with NSCLC, potentially transforming the therapeutic landscape. Next-stage study should focus on optimizing target selection, improving linker technology to enhance stability,and so on,as well as exploring combination strategies with immunotherapy or targeted therapy, thereby promoting the development of individualized therapy.

Keywords: Targeted treatment, NSCLC, antibody drug conjugate.

1. Introduction

As a major public health concern, lung cancer which called "deadly culprit" has persistently risen occurrence frequency and fatality proportions, both in China and globally. Every year, a large number of patients suffer from it, seriously affecting their quality of life. Although the early-stage NSCLC patients have the possibility of being cured after standardized treatment, about 3/4 of them are already in the advanced stage when they are diagnosed, facing a very low survival rate and a heavy treatment burden, which is not only torture to the patients' bodies, but also a test to the patients' psychology and the family's economy. At present, although chemotherapy, targeted therapy, immunotherapy and other traditional therapy methods are widely used in the treatment of NSCLC, there are still problems such as drug resistance and serious adverse reactions. ADC is a new type of drug for the treatment of NSCLC, which has been developed rapidly in recent years. It can precisely target tumor cells like a biological missile and rapidly deliver the drug into the tumor cells, minimizing the attack on normal cells and providing a safer and more effective treatment option for NSCLC patients. This paper

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endeavors to elucidate the structural composition and functional principle of ADCs, along with the challenges encountered. Furthermore, it will provide an overview of the advancements in clinical investigations concerning ADC drugs for NSCLC and anticipate how ADC would develop in NSCLC in order to serve as a guide for the therapeutic management of NSCLC.

2. The working principle and ingredients of ADC drugs

ADC is a type of anti-tumor drug that is both extremely effective and low toxicity. It is composed of monoclonal antibody and cytotoxic medication, which is connected by a linker.

Human immunoglobulin G (lgG) is the most frequently employed monoclonal antibody. It is capable of recognizing the pertinent antigens on the outer membrane of cancerous cells and delivering cytotoxic medications to the interior of the cells to induce their death. Under ideal conditions, monoclonal antibodies originating from ADCs possess the ability to precisely target antigens, these antigens characterized by low or absent expression on healthy human body cells and high expression exclusively on tumor cell surfaces, killing tumor cells efficiently and reducing the damage to healthy cells, effectively reducing toxic side effects.

Cytotoxic drugs are potent chemotherapeutic agents in ADCs that are effective against tumors. Cytotoxic drugs have three different types. The classification is based on their underlying mechanisms of action: DNA damaging agents; tubulin inhibitors which can prevent cell division, such as maytansine derivative emtansine (DM1), maytansinoid (DM4) and monomethyl auristatin E(MMAE); and topoisomerase inhibitors that interfere with DNA synthesis and replication, such as exatecan derivative deruxtecan(DXd) and camptothecin derivative (SN-38) [1].

The connecting moiety, characterized by its exceptional stability, serves as a bridge linking cytotoxic agent to antibody. This bridge can enable ADC to maintain a certain level of stability during the cycling process and can also facilitate the rapid and effective discharge of the chemical that is cytotoxic into the neoplastic cell or tumor microenvironment. Drug-antibody ratio (DAR) is a key parameter affecting the therapeutic effect of ADC, signifying the proportion of drug molecules to antibody molecules, and too much DAR might cause the payload to release too soon, increase off-target toxicity, and harm healthy tissue with harmful side effects. Linkers have two types with different functions. The cleavable linker can produce killing effect through crossing the membrane when it is in the presence of a high concentration of protease, low PH or redox tumor microenvironment, and it can attack the surrounding tumor cells that are not directly targeted with antigen that low or no expression, thus realizing the bystander effect of the drug, which greatly improves the therapeutic effect, but there is a possibility of injuring to normal cells. The non-cleavable linker enters into the interior of tumor cells through endocytosis, which can ensure the stability of the drug in the circulatory process.

Antibodies in ADCs bind to antigens present on the exterior surface of tumor cells to form ADC-antigen complexes and the complexes enter the interior of tumor cells through endocytosis. Under the action of lysosomes and other cellular organelles, the connecting bonds of ADCs are broken and rapidly cleave and release the cytotoxic drugs, which can be circulated freely in tumor cells and affect cell proliferation, thus causing apoptosis of tumor cells. Cytotoxic drugs with permeability will reach neighboring cancer cells through the diffusion method to produce a killing effect and realize the bystander effect.

3. ADC in NSCLC

HER2, HER3, TROP-2, and MET are the primary therapeutic goals for NSCLC therapy.

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3.1. HER2

The HER2 protein exhibits kinase activity associated with amino acid sequences and constitutes one of the four subfamilies within the HER receptor family. Genetic alterations of the HER2 gene, which can be classified into three principal categories, encompass mutations, overexpression phenomena, and gene amplification events. In the treatment of NSCLC, the main drugs targeting HER2 are T-DM1 and T-DXd.

T-DM1 represents the pioneering ADC mainly used for curing advanced-stage HER2-overexpressing NSCLC. This therapeutic agent is characterized by the covalent linkage of trastuzumab to the tubulin inhibitor. The findings of a phase Ⅱ investigation targeting HER2 mutation advanced NSCLC, eighteen individuals had T-DM1 therapy for a duration of three weeks.Among the results,the mPFS was about 150 days, the mDOR was about 120 days, and 44% of patients had an ORR [2]. In another second-period clinical trial, although a high ORR (38.1%) was observed, the mPFS was only 2.8 months, and patients experienced grade 3 adverse reactions (about 18%), such as thrombocytopenia,etc [3]. Moreover,the research data did not demonstrate a more satisfactory therapeutic effect, but all of them indicated the therapeutic potential of T-DM1 to a certain extent.The National Comprehensive Cancer Network recommendations advocate using T-DM1 as a subsequent therapy option for individuals with HER2 mutations.

T-DXd is an ADC targeting HER2 overexpression in advanced NSCLC patients, which consists of a cleavable linker, trastuzumab and topoisomerase I inhibitor .The DAR is 8. A phase Ⅱ DESTINY Lung01 (NCT03505710) clinical trial demonstrated that T-DXd has satisfactory efficacy in patients with refractory HER2-mutated NSCLC who did not respond well to standard therapies. 91 patients received 6.4 mg/kg T-DXd monotherapy; the ORR was 55%, the mPFS was approximately 240 days, the mDOR was 1 month higher than Mpfs and mOS was about 540 days [4]. The prevalent adverse reactions encompassed gastrointestinal toxicity as well as hematological toxicities, notably including neutropenic complications and hematologic anemia manifestations. Although the majority of adverse reactions can be effectively managed, hematological toxicities, necessitate vigilant surveillance. These adverse effects may give rise to detrimental outcomes, such as heightened susceptibility to infections and a decline in patients' quality of life. Consequently, future clinical investigations should prioritize the exploration of strategies aimed at mitigating the incidence and severity of these adverse reactions. Furthermore, the therapeutic efficacy of T-DXd may exhibit variability across distinct patients. Therefore, it is imperative to delve deeper into understanding the underlying mechanisms of action and resistance patterns associated with T-DXd, with the ultimate goal of formulating more precise therapeutic regimens. To facilitate its widespread adoption in clinical practice, it is essential to conduct additional large-scale or Phase III clinical trials to substantiate its efficacy and safety profile.

3.2. HER3

HER3-DXd has a DAR of 4; anti-HER3 antibody and topoisomerase I inhibitor DXd are the components that make up the HER3-DXd medication, which is an ADC medicine that targets HER3.The HER3-DXd was designated as a breakthrough treatment by the FDA after a phase I trial showed promising therapeutic results (NCT03260491) in December 2021. In NSCLC patients had treated with EGFR-TKI before and these patients accepted 5.6mg/kg HER3-DXd, the DCR was 72%, the mPFS was about 240 days, and the ORR was 39% [5]. Stratified analysis showed that the ORR of individuals who had undergone chemotherapy with platinum-based (PBC) drugs (n=44) and osimertinib treatment could reach up to approximately 40% and the DCR was 68%. In addition, research in the second phase (NCT04619004), implement therapeutic interventions for patients with analogous clinical histories, and with a mean of 5 months for mPFS and about 1 year for mOS, the

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ORR of 225 patients given 5.6 mg/kg of the medication was about 29% (approximately 65% and 29% of patients experienced ⩾3 and 4 grade adverse reactions, respectively) [6]. Therefore, it can be seen that HER3-DXd shows favorable clinical effects in patients who have undergone EGFR-TKI and PBC regimens.

3.3. TROP-2

NSCLC is one of the numerous malignancies that exhibit elevated expression of the transmembrane glycoprotein TROP-2. ADCs that target TROP-2 with good therapeutic efficacy for the therapy of terminal-stage NSCLC include IMMU-132 and Dato- DXd.

IMMU-132 is the first ADC against the Trop2 target, which is composed of an anti-TROP-2 monoclonal antibody and a topoisomerase I inhibitor SN-38 linked by cleavable linker, with a DAR of up to 7.6. In the IMMU-132-01 clinical trial encompassing both Phase I and Phase II stages, a cohort of 54 patients was administered varying doses of the medication, specifically 8 mg/kg, 10 mg/kg, or 12 mg/kg [7]. The trial outcomes revealed an ORR of approximately 17%, a DOR averaging 6 months, a PFS period of about 4.5 months, and an OS duration of about 7 months. The findings from this study do not merely underscore the therapeutic effectiveness of IMMU-132 within particular patient subsets; they also furnish a crucial foundation for selecting appropriate dosages in forthcoming clinical trials. Despite the promising efficacy outcomes observed in this trial, the drug's safety profile remains to be thoroughly substantiated. Consequently, future clinical investigations should prioritize a more exhaustive evaluation of the drug's safety aspects, with the aim of ensuring its secure and effective utilization in broader clinical settings.

Dato-DXd(6 mg/kg) was demonstrated to have superior effectiveness and higher safety in the TROPION-PanTumor01 trial [8].The Dato-DXd ORR for 4, 6, and 8 mg/kg in treating the majority of NSCLC patients previously administered immunotherapy and chemotherapy based on platinum were 24%, 26%, and 24%, respectively.It took about 7 and 11 months for the mPFS and mOS to be achieved with Dato-DXd (6mg/kg),respectively, with a DCR of 70%. Therefore, in the TROPION-Lung01 clinical trial in the third phase, the optimal dosage was established as 6 mg/kg [9]. In 2023, the TROPION-Lung02 research results were disclosed by the ASCO, there exist disparities in therapeutic efficacy across various treatment modalities concerning ORR and PFS. While monotherapy exhibits a degree of clinical efficacy (ORR of 38%), the combination therapy approach markedly enhances therapeutic outcomes. Notably, the amalgamation of ADC therapy, immunotherapy, and PBC (ORR of 49%) offers preliminary evidence of the synergistic benefits derived from this regimen. Furthermore, the fundamental combination therapy (ORR of 50%, PFS of approximately 8 months) substantiates this observation. It is pertinent to highlight that despite the triple-drug regimen achieving a notable improvement in ORR (57%), it does not confer a statistically significant extension in PFS (7.8 months). Considering the limitations of this study, including the constrained sample size and the absence of long-term survival outcomes, it is imperative to design a prospective, randomized controlled trial (RCT) in future investigations. Such a study would enable a more robust validation of the current findings and facilitate the derivation of clinically actionable conclusions.

3.4. MET

The microtubule polymerization inhibitor MMAE, a cleavable linker, and an anti-MET antibody make up Teliso-V. Preliminary therapeutic efficacy was noted in a clinical investigation involving only Teliso-V for patients exhibiting pronounced c-Met overexpression.Specifically, the ORR reached 23%, with a mDOR extending to approximately 9 months and a mPFS of 5.2 months [10].In a follow-up study targeting non-squamous EGFR wild-type form of NSCLC patients, the efficacy of

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Teliso-V was verified again in individuals exhibiting elevated cMet expression levels.These findings underscore the potential utility of Teliso-V in specific patient populations and collectively substantiate the decent clinical effect.

4. Problems faced in ADC drugs therapy for NSCLC

ADCs, as new type of anti-tumor agents, have shown progress in many aspects and good therapeutic effects, but they also face some challenges. High DAR or linker instability may cause early release of the drugs and lead to off-target effects, increasing the toxic side effects of the drugs on the human body. Due to the powerful toxicity of the chemotherapeutic drugs themselves, severe cases may lead to treatment interruption or even death. Target antigens are also expressed in normal cells, and toxic loads are released again after they play a part in tumor cells and so on, all also the cause of adverse effects. Improving the coupling technology of ADCs, optimizing DAR, refining the stability attributes of the linker and facilitating the conjugation of cytotoxic agents to more stable sites for subsequent controlled release are effective ways to reduce side effects. In addition, tumor cells can also develop some resistance to ADCs. Down-regulation or loss of antigens targeted by ADCs in tumor cells, deletion of internalization pathways, and increased expression of drug efflux pumps by tumor cells are all reasons for the development of pharmacological resistance [11].

5. Conclusion

ADCs act as innovative anticancer medications that have demonstrated distinct therapeutic benefits and a wide range of potential uses in the treatment of NSCLC. At present, a number of ADC drugs targeting NSCLC have entered the clinical research stage, and evidence-based evidence shows that ADCs show good therapeutic effects and good safety in the treatment of NSCLC and raise the standard of living for patients. Nevertheless, the current research on ADC in the treatment of NSCLC still has certain limitations. First of all, the sample sizes of existing clinical studies are generally small and a scarcity of data from large-scale trials with randomized control exists. The quality of most evidence-based evidence needs to be improved. Secondly, the research progress of ADC drug studies for different targets is uneven, and some potentially important targets have not been fully explored. In addition, the long-term safety and resistance mechanisms of ADCs still need to be further elucidated.

Future research should focus on the following directions: First, larger randomized controlled clinical trials are needed to be carried out to confirm the efficacy and safety of ADCs. Study design should focus on including a more representative patient population and the use of standardized efficacy assessment indicators. Second, comprehensive research on ADCs' mode of action has to be improved, including the process of drug internalization, the mechanism of load release, and the molecular basis of drug resistance generation. These studies will provide a theoretical basis for optimizing ADC structure design. At the technical level, there is a need to develop more stable linker technologies, explore novel cytotoxic loads, and maximize the level of antibody humanization to enhance the ADC therapeutic value even more. Moreover, combination therapy is another important research direction. ADC combined with immune checkpoint inhibitors, targeted drugs or other therapeutic modalities may be able to produce synergistic effects, and the exploration of these combination options needs to be based on a profound comprehension of the mechanism working and validated through rational clinical trial design. With the research development,it is believed that ADCs will play a more significant role in the treatment of NSCLC.

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