Antibody-Drug Conjugates in NSCLC and SCLC

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Abstract. Lung cancer, the most prevalent type of cancer, would likely account for 1.8 million cancer deaths (18%) worldwide in 2020. Non-small cell lung cancer (NSCLC) is more common in clinically diagnosed patients, whereas small cell lung cancer (SCLC) is less common but typically develops more quickly. However, traditional treatment methods, such as surgery, adjuvant chemoradiotherapy, have their limitations. Antibody-drug couplings (ADCs), one of the fastest growing cancer drugs of late, use exclusive binding of their monoclonal antibodies (Mabs) to the surface antigens of cancer cells to precisely deliver anti-cancer drugs to target cancer cells. ADC, which specifically targets cancer cells while preserving healthy ones, is a promising cancer treatment. Five ADCs approved by the FDA for solid malignancies, while numerous ADCs targeting NSCLC and SCLC are globally in number of clinical trials. This article reviews the therapeutic use of ADC in non-small cell lung cancer and small cell lung cancer. Develop an understanding of the mechanisms and clinical effects of ADCs.

Keywords: Non-small cell lung cancer; small cell lung cancer; Antibody-drug couplings; monoclonal antibodies.

1. Introduction

At present, the clinical treatment of cancer mainly relies on surgical treatment and adjuvant chemoradiotherapy, and the treatment methods for different pathological types of cancer, different blood system tumors or solid tumors are completely different. The most routine surgical treatment is the most commonly used in clinical treatment. The surgical method can remove cancer cells, slow down the spread and metastasis of cancer cells, and the treatment effect is better. However, the problem of large trauma and high recurrence rate cannot be ignored. Similar to surgery, chemoradiotherapy has its own advantages and disadvantages. One of the anticancer medications that is evolving the fastest is called antibody-drug conjugates (ADCs). The ADC included three components: the antibody that will kill the targeted cell, the linker, and the cytotoxic agent. Therefore, ADCs can precisely deliver anticancer drugs to the target cancer cells, utilizing the exclusive binding between monoclonal antibodies (mAbs) of ADC and surface antigens on the cancer cells.

Traditional chemotherapy medications target fast-dividing cells to achieve their desired effects, including cancer cells and normal healthy cells. This non-selective action leads to a range of severe side effects, making patients suffer and debilitating. ADCs enhance efficacy and reduce toxicity in treating cancer by selectively delivering potent drugs to tumor cells while sparing healthy cells. Therefore, ADCs are a valuable addition to the arsenal of treatment options available to patients with cancer.

The most frequent cancer to be diagnosed is lung cancer which is predicted to cause 2.2 million patients, as well as result in 1.8 million mortalities in 2020, according to the World Health Organization report. Lung cancer is broadly categorized into two main types based on the characteristics of cancer cells: NSCLC and SCLC. About 85% of occurrences of lung cancer are NSCLC, while SCLC makes up the remaining 10-15% of cases and spreads more swiftly [1].

ADCs have not yet received FDA approval for lung cancer treatment. This review's first part will overview promising ADC in NSCLC and SCLC, then discuss challenges and possible solutions in developing ADCs treating lung cancer.

2. ADCs target NSCLC and SCLC

2.1. Different ADC targets and therapeutics in NSCLC

Adcs can connect cytotoxic drugs to tumor-targeting monoclonal antibodies, which can be used to improve the targeting of anti-tumor drugs to tumor cells. At the same time, it can reduce the toxic side effects of anti-cancer drugs on the body. The toxic payloads used in the first generation of ADC drugs have limited toxicity. And the joint is unstable. Causing the first generation of drugs to break down in the blood causing serious damage to the body. Researchers improve tumor targeting specificity of second-generation ADC drugs. At present, ADC drugs have been upgraded with three generations of technology, and their stability, drug antibody ratio uniformity, chemical composition production and control characteristics, and anti-tumor activity have been continuously improved, expanding the therapeutic threshold for tumors. At present, ADC drugs are playing an increasingly important role in tumor therapy. ADCs are a fast-developing class of treatments for NSCLC that are now being investigated across a wide range of targets with encouraging preliminary results. The current ADC targets in NSCLC are briefly reviewed in this section, as well as the preliminary efficacy of ADC medicines such T-DXd and Teliso-V, which are covered individually below.

2.1.1. Traztuzumab deruxtecan (T-DXd)

The FDA authorised T-DXd as the first ADC in December 2019 to treat NSCLC with Human Epidermal development Factor Receptor 2 (HER2) mutations [1]. This marker was a protein that controls cell development and division [2]. Therefore, HER2 gene mutation and protein overexpression have the potential to cause lung cancer and unchecked cell development.

Trastuzumab is a mAb that specifically targets HER2. Deruxtecan (DXd) is an inhibitor for novel DNA topoisomerase I, as a chemotherapy payload. DXd is conjuated to the trastuzumab antibody through a stable linker whose exact information is held by the drug's developer, Daiichi Sankyo [3].

There are trials that illustrate the anticancer effectiveness of T-DXd, DESTINY-Lung01 and DESTINY-Lung02. Bob T. Li and his colleagues administered T-DXd to HER2-mutant NSCLC patients in a multicenter, worldwide, phase 2 study of the DESTINY-Lung01 trial. There were 91 patients enrolled in all. 55% of the patients made a confirmed, therapeutic response. The average wait time for a response was 9.3 months. In the meanwhile, the median survival time increased to 17.8 months. Regarding safety, neutropenia (19%) was the most frequent event, occurring in about half of patients (≤ grade 3 adverse events). A set of lung conditions known as interstitial lung disease (ILD), which affects the alveoli in the lungs, occurred in 26% of patients and claimed the lives of 2 of them [2]. The findings of this study demonstrate that T-DXd 5.4mg/kg has long-lasting anticancer effects in HER2-mutant NSCLC patients who were previously treated. To properly treat potentially catastrophic adverse events and determine which individuals are greatly at risk, more research is needed. DESTINY-Lung02 indicate that treatment-emergent adverse events were more likely to be caused by the dose of T-DXd of 6.4 mg/kg than 5.4 mg/kg [3]. DESTINY-Lung02 demonstrated clinically significant effectiveness and had a better safety profile, when the drug was used in 5.4 mg/kg.

2.1.2. Patritumab deruxtecan (HER3-DXd)

Several malignant solid tumours exhibit the receptor tyrosine-protein kinase ERBB3 (HER3), which has been identified in 83% of initial NSCLC tumours. NSCLC is one of many human cancers that have been connected to the pathophysiology of EGFR gene overexpression. In comparison to EGFR wild-type NSCLC, HER3 is expressed more frequently in EGFR-mutated (EGFRm) NSCLC. The indications for NSCLC targeted therapy are thus expanded by HER3. Though the tumour-selective, the anti-HER3 immunoglobulin G1 mAb was attached to the inhibitor payload, cleavable linker in Patritumab deruxtecan (HER3-DXd). The linker is stable in plasma, however because of its brief systemic half-life in circulation, it has less of an adverse effect on the body. Osimertinib, an EGFR tyrosine kinase inhibitor (TKI), growthed HER3-DXd internalisation rates and HER3-DXd's ability to prevent tumour growth in preclinical models of EGFRm NSCLC. Therefore, individuals

with advanced EGFRm NSCLC are evaluating in the phase I clinical trial with HER3-DXd and osimertinib [4]. To further assess HER3-DXd in a broader population of NSCLC patients whose disease has advanced during or after receiving Osimertinib plus one or more rounds of platinum-based chemotherapy. According to the phase I trial results, HERTHENA-Lung01 is in its second phase [5]. The outcomes of the research indicated above will provide more information on the antitumor efficiency and safety profile of HER3-DXd in EGFR-mutant NSCLC patients.

2.1.3. Datopotamab deruxtecan (Dato-DXd)

Tropoblast cell surface antigen 2 (TROP2) is overexpressed in epithelial malignancies. Additionally, it participates in a number of intracellular signalling pathways linked to cancer cell invasion, migration, and proliferation. As a result, TROP2 overexpression is associated with a variety of malignancies, including NSCLC.

Human Immunoglobulin G1 Monoclonal Antibody (IgG1 mAb) Datopotamab (Dato) targets human TROP2. In order to get it, mice were first immunised with human lung adenocarcinoma cells, and then mAbs that internalised into cancer cells were searched for. A unique TROP2 directed-ADC containing Dato-DXd was created by Okajima and his colleagues. The DAR is typically 4. Additionally, the cell proliferation of TROP2-high cell lines was noticeably inhibited in vitro by Dato-DXd, showing that Dato-DXd is efficient in preventing the spread of tumour cells in a variety of cancer types [6].

In progress, many ongoing studies expect Dato-DXd to be used in combination therapy. A monoclonal antibody called pembrolizumab is employed in cancer immunotherapy. It targets the protein PD-1, which NSCLCs employ to evade the immune system. The TROPION-Lung08 research, a two-armed phase III trial, will assess the advantages and disadvantages of Dato-DXd with pembrolizumab. Another investigation, the TROPION-Lung07 study, compares it with or without platinum as the primary therapy for NSCLC patients who expressed PD-L1 less than 50%. Dato-DXd will have a role to play in patients with NSCLC in the frontier, based on the findings of these studies [7].

2.1.4. Telisotuzumab vedotin (Teliso-V)

c-Met protein overexpression and EFGR mutations happen simultaneously in NSCLC. HGF, known as unconventional c-Met receptor tyrosine kinase, is encoded by the mesenchymal-epithelial transition factor (MET) gene. HGF, a heparin-binding protein on epithelial and endothelial cells, displays strong mitogenic, motogenic, and morphogenic activity. A poor prognosis in lung cancer has been linked to overexpression of c-Met, according to earlier research [8]. Consequently, c-Met and EFGR dual targeting is viable for treating NSCLC.

The anti-c-Met mAb ABT-700 is joined to cytotoxic inhibitor through the cleavable linker to create Telisotuzumab vedotin (Teliso-V), a cutting-edge ADC targeting c-Met. The DAR of Teliso-V is 3.1. In the Phase I research, individuals with c-Met-positive NSCLC showed encouraging signs of anticancer activity while receiving Teliso-V monotherapy [9].

More recently, Telisotuzumab Vedotin combined with erlotiniban was conducted in c-Met protein-expressing (c-Met+) NSCLC patients. Erlotiniban is an EGFR tyrosine kinase inhibitor, 42 patients were enrolled. The majority of adverse events, or 24 out of 42 patients (57%) who reported them, were neuropathies. Teliso-V + erlotinib had a comparable pharmacokinetic profile to Teliso-V used alone. For all patients whose efficacy could be evaluated, the median length of time that disease does not progress during and after treatment disease was 5.9 months. For EGFRm patients, the objective response rate was 32.1%. This finding demonstrates that the combination of Teliso-V with erlotinib, particularly EGFR TKIs failed patients, offers a favourable safe and antitumor efficacy in patients who have had a significant amount of prior therapy [10].

2.2. Different ADC targets and therapeutics in SCLC

The landscape of ADCs' treatments for (SCLC) is likewise changing. DLL3, CD56, and TROP-2 have been considered potential candidates for creating ADCs. ADC that targets DLL-3,

rovalpituzumab tesirine, did not improve efficacy results when compared to topotecan or when used as maintenance following first-line therapy [11]. Sacituzumab govitecan has also been analyzed in 62 patients with refractory SCLC included in the IMMU-132-01 trial [14]. However, due to the low incidence of SCLC compared to NSCLC, the progression is not as much as NSCLC. Below this part will review the details of other successful (ABBV-011, I-DXd) and failed (LOP628) ADCs in SCLC.

2.2.1. ABBV-011

ABBV-011, an ADC targeting seizure-related homolog protein (SEZ6) with calicheamicin payload, demonstrated antitumor influence in the phase 1 trial of refractory SCLC patients. Seizure-related protein 6 is a protein that is encoded by the SEZ6 (Segmental Duplications, Zinc Finger Protein 6) gene. SEZ6 is a highly expressed surface marker in SCLC with little expression in normal tissue. A powerful DNA-damaging chemical that causes toxicity in a variety of cell types is calicheamicin. As a result, calicheamicin has been utilised in cancer as an ADC payload [12].

The objective of this phase I clinical study were to assess the drug's safety to establish the drug's optimal dose and suggest the dosage used in phase 2. Participants were adults with relapsed or resistant SCLC. Patients who had been chosen by SEZ6 underwent dose expansion. 99 patients received ABBV-011, 50% were men, the median age was 63, and 68% had previously undergone two or more therapies. The pharmacokinetics of the ABBV-011 ADC were roughly proportional to the dose. Its elimination half-life is 4.6 days. The mean treatment time was 12 weeks; the range was 1.9 to 63.3.

39 patients (98%) had treatment-emergent adverse events (TEAEs), and 18 (45%) patients experienced grade 3 TEAEs. One patient experienced grade 4 TEAEs, including dyspnea. The growth of malignant neoplasm diseases or respiratory distress claimed the lives of seven victims. No one was associated with ABBV-011. With a median response time of 4.2 months, without advancement was 3.5 months. Therefore, ABBV-011 was well tolerated and showed encouraging anticancer efficacy. The assessment of ABBV-011 is still being done [13].

2.2.2. Ifinatamab deruxtecan (I-DXd)

Immune checkpoint inhibitors have demonstrated notable impacts on solid cancers in recent years. Immune escape and immune evasion are caused by the B7 molecules in the tumor microenvironment. B7-H3 is a type I transmembrane protein. ADC targeting B7-H3 was created because of studies showing that B7-H3 has a poor prognostic impact on SCLC [14]. Ifinatamab deruxtecan (I-DXd) is a brand-new ADC that combines a humanised anti-B7-H3 IgG1 mAb with an inhibitor payload. Daiichi Sankyo is conducting Phase II trials of I-DXd treating SCLC. The phase transition success rate (PTSR) indication standard for Phase II medicines for SCLC is 26%, according to GlobalData.

2.2.3. LOP628

c-KIT is a receptor tyrosine kinase in intracellular signalling and is encoded by the KIT gene. C-KIT’s mutated and overexpressed forms play a crucial role in oncogenesis, including SCLC and NSCLC. Therefore, Abrams’ team tried to evaluate the anticancer activity of the c–KIT–directed ADC, LOP628, for the treatment of SCLC. LOP628 consists of the microtubule-destabilizing payload DM1, the humanised anti-c-KIT antibody LMJ729, and a non-cleavable linker, SMCC. In vitro and in vivo tests were proceeded on LOP628's anti-SCLC model activities [15].

On c-KIT-positive cell lines that expressed SCLS in vitro, LOP628 caused mitotic arrest and demonstrated strong antiproliferative activity (NCI-H1048, NCI-H526). With a sufficient therapeutic index many folds above effective exposures, LOP628 was well tolerated in vivo in monkeys. Therefore, according to the preclinical results, the ADC targeting c-KIT, LOP628 could be an effective therapy to treat SCLC. Successful preclinical outcomes are difficult to translate into clinical safety, though. The mast cell degranulation that is thought to be the cause of the clinical acute hypersensitivity events reported during phase I clinical trial was not predicted by the monkey research. According to the sponsor, Novartis Pharmaceuticals, this programme has been terminated since 2015.

3. Problems of ADCs and possible solutions

Even though the theoretical understanding of ADCs has dramatically increased. They have a few drawbacks. It is possible for cells other than the target cancer cells to interact with the cytotoxic payload of the ADC, which could lead to unanticipated interactions or outcomes. These off-target effects can lead to TEAEs and other consequences, such as those mentioned above. ADCs can nevertheless cause a range of damaging and even deadly toxicities. Off-target effects cause most of these toxicities.

Various linking techniques have been useful in reducing off-target effects by enhancing drug transport to the cancer location. The ability of an ADC to traverse a blood artery is hindered by an antibody's high molecular weight. Additionally, a fragmented antibody or a different type of mAb can aid in lowering molecular weight. The effectiveness of delivering the payload to the cancer site can also be improved by using this alternate mAb type.

Furthermore, delivering ADCs into solid tumours is very challenging due to the antigen barrier. A failed internalized ADC should be taken into account for the treatment of solid tumours. These failed internalized ADCs release their payload into the tumour microenvironment, where it will diffuse into the cell and enter, where it will trigger cell death.

Furthermore, an ADC with a dual payload is more effective in killing cancer cells and has a higher DAR. Other techniques included non-covalent DNA conjugation of the payload and the antibody. With a 5.8-day half-life, this tactic reduces the hazardous payload's overall hydrophobicity.

4. Conclusion

In conclusion, most of the ADCs for lung cancer are ongoing trials to test their efficacy by targeting different mutated and overexpressed proteins that occur in lung cancer. T-DXd HER3-DXd, Dato-DXd, and Teliso-V have shown some potential in preclinical and early clinical trials for treating NSCLC. In order to determine their long-term advantages, safety, and perspective, more research is being done. The failure of LOP628 to cure SCLC led to advancements in ABBV-011 and I-DXd by researchers. Early-stage clinical trials of ABBV-011 in SCLC patients have shown promise, although I-DXd lacks open experimental trials demonstrating its efficacy. However, an ADC's pharmacology is intricate and may include toxicities. Therefore, for the development of this discipline, a thorough understanding of the components that have an impact on ADCs is essential. Scientists can construct ADCs with maximal efficacy by considering stability, the target expression effects, and the environment of disease. Patients with lung cancer will benefit from better treatment outcomes and more therapeutic alternatives as a result.

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