Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 3
BLSME 2024

Utilization of New Methods for Antibody Drug Conjugates: Research Progress and Future Prospects

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Abstract. Cancer has become an obvious health problem and scientists focus on this to help the problem. Antibody drug conjugates (ADC) has been considered as an efficient way to treat cancer. There are already many ways to produce ADC, but traditional methods need long and complicated biochemical process. Synthesis methods with high efficiency need to be found. This article aimed to describe three new methods for ADC synthesis, and it came out that all these three methods have high quality and can be used as a common technology to produce ADC. Also, the safety of ADC and several examples of clinical use for ADC were introduced. It provides a reference for ADC synthesis in a relatively simple chemical process for future research. However, there are still some chemical problems that have not been solved, such as azide derivatives are not easy to obtain and they are not stable enough. Future research can focus on the properties of azide derivatives direction.

Keywords: ADC; click chemistry; scale-up synthesis; flow reactors.

1. Introduction

Now ranked as the second biggest hazard to global health, cancer has caused 10.0 million deaths worldwide in 2020. Scientists have been developing novel cancer therapies with improved targeting capacity in an effort to overcome this problem [1]. Antibody drug conjugates (ADC) employ the antibody's selectivity to direct the poisonous payload toward tumor cells. ADCs are injected intravenously, go into the bloodstream, spread to tumor tissues, and attach themselves to the antigen on the tumor surface. After internalizing the ADC into tumor cells through endocytosis, the antigen is transferred to lysosomes, where the payload is released. By damaging DNA or inhibiting microtubules, the toxic payloads that are released can cause apoptosis, and they can also kill nearby cancer cells by causing the bystander effect [2].

Paul Ehrlich first put out the idea of "magic bullets" at the start of the 20th century, speculating that certain substances might directly target specific cell targets to treat illnesses. In theory, these substances ought to be efficient in eliminating cancerous cells while remaining innocuous to healthy cells. Finding a few particular overexpressed antigens to differentiate cancer cells from healthy cells is one of the conceivable methods. When these antigens are expressed specifically, monoclonal antibodies (mAbs) can be used to precisely target tumors; this field has improved significantly since the invention of hybridoma technology in 1975 [1].

In 1983, the concept of “magic bullets” had been used to accomplish the first ADC treatment human experiment. Further developments in antibody, linker, and payload technology have prompted the creation of ADCs that, in comparison to previous attempts, have better selectivity for cancer cells, less immunogenicity, and increased potency and serum half-lives [3].

The ADC era of cancer targeted treatment began in 2000 when the U.S. Food and Drug Administration (FDA) authorised Mylotarg (gemtuzumab ozogamicin) for use in people with acute myeloid leukaemia (AML). As of December 2021, 14 ADC drugs had been approved globally for solid tumours and haematological malignancies. Furthermore, more than 100 ADC candidates are now undergoing various phases of clinical studies. With its growing targets and indications, the ADC drug's historic journey from an infant to a mature development stage over the past 100 years was

illustrated. ADC is spearheading a new era of targeted cancer therapy and is anticipated to eventually replace traditional chemotherapies.

Although several ADCs have been approved by FDA and new developments appear in the research of ADCs, there is still great potential in this aspect with the development of technology. Based on recent research on ADCs, this article analyses some methods of the synthesis of ADCs in order to show the access to ADCs in clinics. A few applications of ADC are shown and this will offer new ideas for the design and improvement of ADCs for future research.

2. Synthesis

As for the important use of ADCs, how to get ADCs that can be used in clinics has become a kind of trending topic. ADCs can be produced in chemical process. This article illustrates three methods of the synthesis of ADCs: click chemistry, scale-up synthesis and Continuous Flow Microreactor Technology.

2.1. Click Chemistry

Click chemistry is a relatively new method of chemical synthesis in organic chemistry. Click reaction mainly refers to a kind of reaction with the characteristics of high yields, low byproducts, high selectivity, not sensible to water and oxygen, moderate reaction conditions, wide selection of substrates and simple post-processing. Click reactions are a class of high-speed, efficient, high-yield reactions that generate a single column-free product that is stereoselective and easy to operate. As for these characteristics, click reactions have been applied to pharmacy in order to produce complicated structure that are difficult to produce by traditional chemical and biological processes.

Despite of the advantages of ADC, it is not an easy thing to obtain ADC because of its structure. However, if click chemistry can be applied to the process of producing ADC, it will increase ADC in clinic. Totally ADC production of click reactions is cycloaddition which is a classic reaction in modern chemistry, such as Diels-Alder reaction ([4+2] cycloaddition with substrates as dienes and alkenes). In the production of ADC, the [3+2] cycloaddition is mainly used with copper(I) as catalyst. Erol C. Vatansever et al discovered a versatile reaction for bioconjugation as Cu(I)-catalyzed alkyne-azide cycloaddition (CuAAC) [4]. It is mainly about reactions with azide and Coumarin derivatives. This study mainly concerned with different substrates and ligand to stabilize copper(I). The result showed that it was an access to produce ADC.

2.2. Scale-up Synthesis

Scale-Up Synthesis is another option to produce ADC. This method aims to overcome the heterogeneity drawback of current ADC. Tomohiro Watanabe et al reported a novel Fc-affinity peptide-mediated conjugation method, termed AJICAP second-generation. This study is mainly concerned with peptides under different reaction conditions and scale-up synthesis for two peptide reagents. This had a yield over 80% in target drug to antibody ratios (DAR). The consistency of DAR and aggregation rates could be reliably recreated across several scales, as confirmed by the use of different scales in ADC synthesis. The findings clearly show that the AJICAP second-generation procedure is a reliable and useful method for producing ADCs [5].

2.3. Continuous Flow Microreactor Technology

This is a considerably new method in chemical engineering. Chemical reactions can take place inside protected pipes and tubes thanks to continuous flow reactors. Some of the drawbacks of batch reactors, which are often utilised, are thought to be addressed by this synthetic approach. Though ADC synthesis has been reported as continuous flow reactor, it does not become a popular method and has many limitations. Yuichi Nakahara et al focused on the production of ADC by continuous flow reactors and this study mainly discussed production factors such as the optimized mixer type, reaction

time, and mixer diameter [6]. Results showed that Continuous Flow Microreactor Technology is an accessible way to produce ADC.

3. Application of ADCs

3.1. Sacituzumab Govitecan

Sacituzumab govitecan (SG), an ADC targeting the TROP-2 protein, represents a significant advancement in breast cancer treatment, addressing both Triple-Negative Breast Cancer (TNBC) and Hormone Receptor-positive (HR+) subtypes [7]. TROP-2, a transmembrane glycoprotein involved in various cell signalling pathways including calcium transduction and MAPK signalling, is overexpressed in various cancers, including breast cancer, where its elevation correlates with poorer survival outcomes. SG, comprising a humanised anti–TROP-2 monoclonal antibody linked to SN-38 (an active metabolite of irinotecan), exploits TROP-2 to deliver potent cytotoxicity directly to cancer cells.

SG's design offers several advantages, making it uniquely suited as an ADC. Its active metabolite, SN-38, is substantially more potent than irinotecan and capable of a ‘bystander effect’ due to its membrane permeability. Additionally, SG’s hydrolysable linker facilitates both intracellular and extracellular release of SN-38, enhancing its therapeutic potential, especially in tumours with heterogeneous TROP-2 expression. Notably, SG maintains a high drug-to-antibody ratio (DAR) of 7.6:1, surpassing previous ADCs like T-DM1, which enhances its efficacy without compromising pharmacokinetics or antibody binding.

In TNBC, early clinical trials demonstrated SG’s efficacy, with the IMMU-132-01 trial (NCT01631552) reporting significant partial responses in patients receiving 10 mg/kg of SG [8]. The subsequent ASCENT trial (NCT02574455) compared SG with single-agent chemotherapy, revealing SG’s superior therapeutic effect in TNBC patients with at least two prior lines of chemotherapy.

The success in TNBC led to the evaluation of SG in metastatic HR+/HER2- breast cancer. In the IMMU-132-01 trial, patients showed a noteworthy overall response rate (ORR) of 31.5% and a median duration of response (DoR) of 8.7 months, indicating SG’s potential efficacy in this breast cancer subtype.

3.2. In Epithelial Cancer

A study on the use of SG in epithelial cancer, following methods similar to the IMMU-132-01 trial used in breast cancer, provides insights into the application of ADCs in a broader oncological context. This study involved patients aged 18 and above with metastatic epithelial cancer who had relapsed or were refractory to at least one standard therapeutic regimen. The course of treatment was giving SG intravenously on days 1 and 8 of 21-day cycles at dosages of 8, 10, 12, or 18 mg/kg. The infusions were given until the disease progressed, the toxicity became intolerable, the patient passed away, or the consent was withdrawn [9].

The study assessed the exposure to SG by evaluating treatment duration, doses, and cycles. It also recorded instances of treatment interruptions and discontinuations. Specifically, treatment delays were defined as exceeding 28 days between the first and second dose of the same cycle, or more than 35 days between the second dose of one cycle and the first dose of the subsequent cycle. The safety of SG in the overall study population (OSP) was monitored through adverse events (AEs), laboratory assessments, physical examinations, vital signs, and electrocardiograms.

495 patients were included in the OSP, with a majority being female (67%) and white (82%), and a median age of 61 years. Nearly all patients (98.6%) had stage IV disease at screening. Concerning UGT1A1 status, an important factor in the metabolism of irinotecan (a key component of SG), 36% were wild type, 36% heterozygous, and 9% homozygous. The median follow-up time was around 9

months. At the time of analysis, treatment was ongoing in only 2.4% of patients, with the remainder having discontinued, predominantly due to disease progression (67.7%) and AEs (8.3%).

3.3. Trastuzumab Deruxtecan

The evaluation of trastuzumab deruxtecan in non-small-cell lung cancer (NSCLC) reflects a significant development in the application of ADCs for lung cancer treatment. The DESTINY-Lung01 study, a phase 2, multicentre, open-label study conducted across 21 sites in North America, Japan, and Europe, aimed to assess the efficacy and safety of trastuzumab deruxtecan in patients with either HER2-overexpressing or HER2-mutant NSCLC. This study is particularly noteworthy as it focuses on a cohort of patients with a HER2 mutation, a group that has previously shown limited treatment options [10].

Measuring the proven objective response as determined by an independent central review using the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, was the study's main goal. The length of response, progression-free survival, overall survival, and disease control (defined as full response, partial response, or stable illness at 6 weeks without progression) were among the secondary outcomes. In order to assess the time to response and find putative response biomarkers, exploratory objectives were also specified.

The results of the DESTINY-Lung01 study revealed that trastuzumab deruxtecan exhibited durable anticancer activity in patients with HER2-mutant NSCLC who had previously undergone treatment. However, the safety profile of the drug raised concerns due to the incidence of interstitial lung disease, which proved fatal in two cases. The observed toxic effects were generally consistent with those reported in previous studies of trastuzumab deruxtecan.

4. Conclusion

This article totally introduced three new methods for ADC synthesis. One of them was mainly about synthesis method (click chemistry) and the others were mainly about industrial production (scale-up synthesis and continuous flow microreactor technology). Click chemistry offered a highly efficient way for ADC synthesis with advantages such as high yields, low byproducts, high selectivity, not sensible to water and oxygen, moderate reaction conditions, wide selection of substrates and simple post-processing. Click reactions are usually one-step reaction so it is easier to operate and omits the complicated process to synthesis substrates. Scale-up synthesis in ADC succeeded in ADC synthesis with a large scale and provide an access for ADC industrial production. Continuous flow microreactor technology was a new method in chemical engineering to overcome some limitations of commonly used batch reactors and experiments showed that flow reactors were possible for ADC synthesis with high quality. From this research, it can be seen that ADC synthesis has developed into high efficiency and simplified process. And it led to future researches focus on how to make ADC synthesis simpler and more efficient. Limitations of this article were it only concerned one type of ADC reaction with substrates as azide and coumarin derivatives. ADC will gradually become one of the most efficient therapies for cancer and its production will surely become an important topic in chemical engineering.

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