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Review of antibody-drug conjugates in lymphoma therapies

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Abstract. Antibody-drug conjugates (ADCs) are a series of targeted therapeutic agents for cancer treatment and have succeeded in treating various cancers. Over the years, ADCs have revolutionized cancer treatment by offering new options to patients. These agents act as an alternative to traditional chemotherapy and radiation therapy, and many pharmaceutical companies have developed their own ADC drugs. Based on the available materials, this review discusses the fundamental concepts behind the design of ADC drugs for treating lymphoma. It provides a comprehensive analysis of various marketed ADC drugs from multiple perspectives.

Keywords: antibody-drug conjugates (ADCs), cancer therapy, combinatorial strategies, lymphoma.

1. Introduction

Lymphatic cancers, such as non-Hodgkin's inert lymphoma, can be challenging to treat. The most available lymphatic cancer treatment options are chemotherapy, radiotherapy, and immunotherapy, and neither of them are facing significant disadvantages. Although chemotherapy and radiotherapy are relatively effective treatment, the non-specificity always cause significant side effects, including but not limited to nausea and vomiting, fatigue, decreased appetite, changes in taste, hair loss, dry mouth, and constipation [1]. Despite the efficacy and relatively low cost of these treatments, they may cause great suffering for patients [2].

In 1913, German scientist Paul Ehrlich introduced the "Magic bullets", which aimed to provide efficient and targeted treatment using biotechnology [3]. The hybridoma technique was developed using the natural hybridization technique, leading to the creation of the first monoclonal antibodies. The launch of rituximab and trastuzumab in 1990 marked a breakthrough in cancer treatment, as it became possible to target antibodies to cancerous cells through specific binding, known as "Immunotherapy" [4]. However, despite decades of development, the efficacy of immunotherapy remains inconsistent, and its effectiveness is often limited by the patient's immune system [5]. Most patients with low immunity might not experience significant therapeutic effects from the treatment, and there is also a risk of immune inflammation [6]. On the other hand, with the first successful clinical trial of ADC in 1983 and approval of the first ADC drug—Mylotarg—by the FDA in 2000 [7], several companies entered the industry and developed their ADCs. Up to 2022, 14 ADCs have received market approval, and over 100 ADC candidates are in the clinical investigative stage [8].

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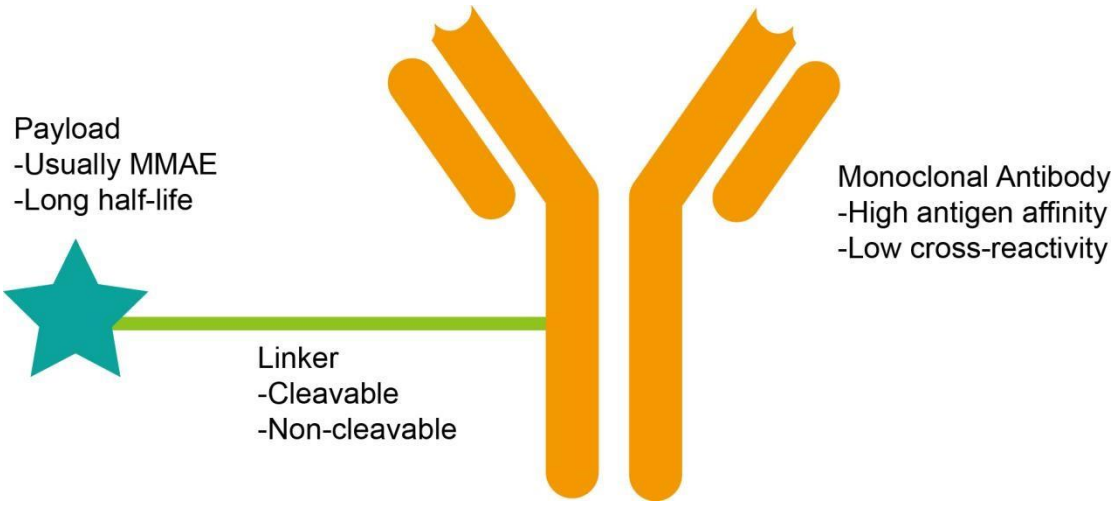

Figure 1. Components of ADCs.

2. ADCs structure

ADC drugs are consisted of three basic units, antibodies, payloads, and linkers.

2.1. Monoclonal antibody (mab)

Monoclonal antibodies (mAbs) play a crucial role in ADC therapy, as they can specifically recognize and attach to tumor cells' antigens, providing a targeted approach for cancer treatment. This specificity and affinity to surface antigens are essential for antibodies to connect to the corresponding cells. Unlike small-molecule therapeutics, which may fail to distinguish the healthy human cell from the tumor cells, ADCs, in this aspect, are pretty advantageous due to their explicitly recognizing ability to the tumor cells' antigens. For antibodies to connect to the antigen-correspond cells, the specificity and affinity to the surface antigens are essential [9]. Generally, it is difficult for drugs to distinguish a normal cell from a normal human cell since their surface antigen is identical. This consistency causes difficulties in choosing the targeted antigen when designing the drugs [10]. However, the invention of monoclonal antibodies and the discovery of tumor-specific antigens changed this in 1970, making it possible to target specific antigens in tumor cells [11].

There are mainly five classes of antibodies found in serum—lgM (Immunoglobin M), IgD, IgG, IgE, and IgA. Responsible for specifically binding to antigens, these antibodies act as the main structure of the ADC. Thus, when selecting monoclonal antibodies for ADC design, it is essential to consider their cross-reactivity and immunogenicity in patients [12]. lgG1 is the most frequently used antibody due to its simplicity in production and low clearance during circulation.

To minimize the risk of adverse immune reactions, humanized (Modified antibodies from non-human species) antibodies and human antibodies are preferred for most ADCs.

2.2. Cytotoxic drugs (payload)

Cytotoxic drugs are expected to possess high stability, weak immunogenicity, and a long half-life since their primary aim is to induce cell death. [13]. ADCs typically utilize microtubule-disturbing or DNA-damaging agents as their payload [14].

2.3. Linker

Since linkers connect the mAb and the payloads, their stability in circulation is essential. To ensure the release of the payloads at the proper time and place, the linker must be efficient enough to be cleavable in target tumor cells as it needs to release the payloads [15]. Linkers could be categorized into two groups-non-cleavable and cleavable—according to their payload release mechanisms [16]. Non-cleavable linkers are relatively stable in systemic circulation as they primarily degrade in lysosomes

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[17]. In contrast, cleavable linkers, as they mainly depend on their physiological conditions, are less stable during systemic circulation [18]. For example, Mylotarg, the first FDA-approved ADCs, uses a linker to release its payload (ozogamicin) when exposed to acidic conditions, leading to severe adverse reactions in some patients.

3. ADCs mechanism of action

ADC drugs are administered into the body through intravenous injection, and bind to antigens on the tumor cell surface. The bound ADCs are then internalized by tumor cells, resulting in endosomes, where ADC molecules bind to Fc receptors (FcRns) in endosomes. The ADC molecule bound to the Fc receptor is re-transported outside the cell. As the pH rises, the ADC molecules separate from the Fc receptors. The ADC drug that is not attached to the Fc receptor is eventually retained in the endosome and transported to the lysosomal compartment, where it is degraded, leading to the release of the cytotoxic drug payload. However, when the ADC drug is injected into the body, there is a loss of ADC drug at each step from blood circulation to cellular internalization. Without sufficient cytotoxic molecules released into the cell, eventual apoptosis cannot appeal. Therefore, maximizing the efficiency of each step is crucial for the overall effectiveness of ADC therapy.

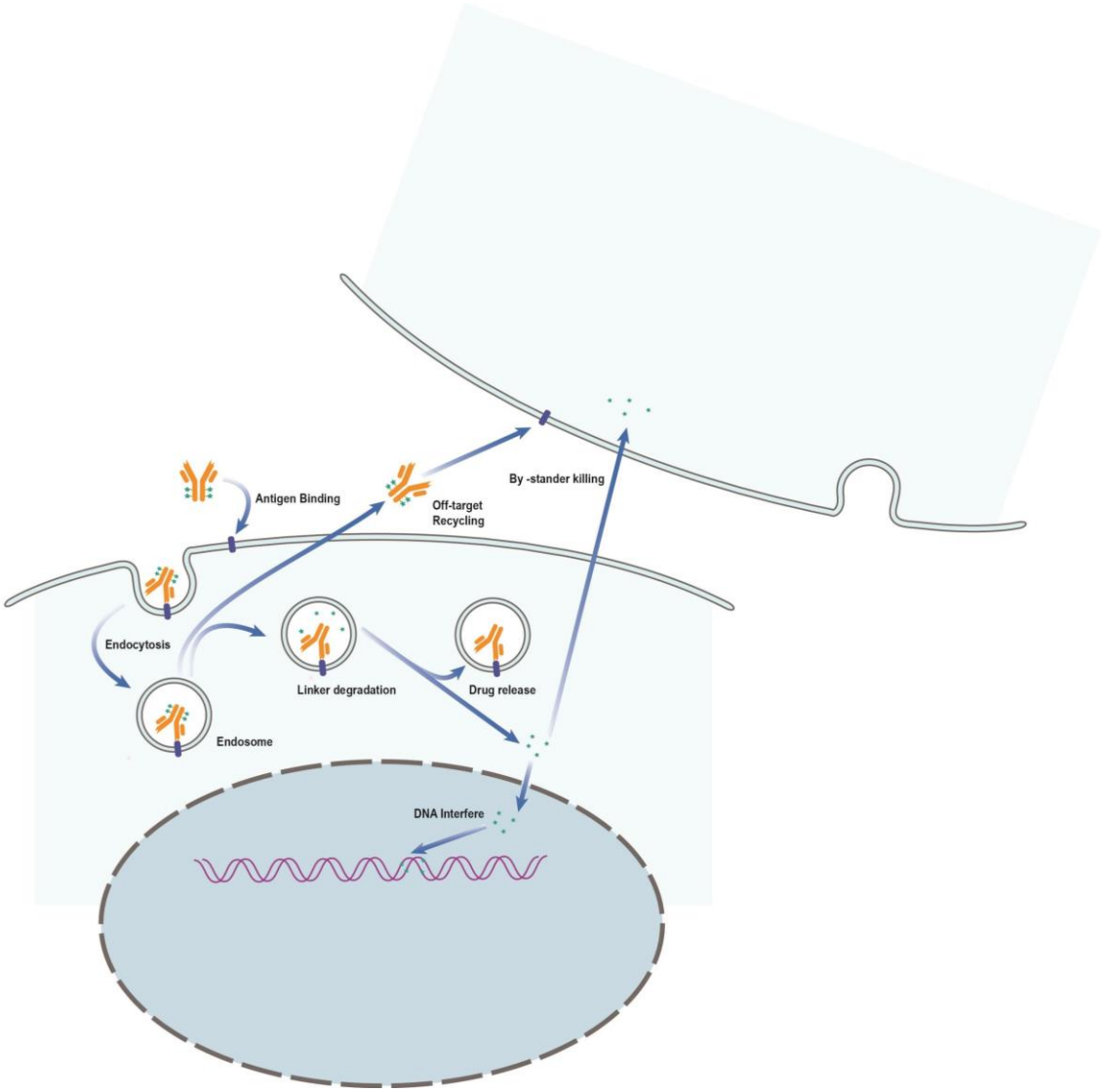

Figure 2. Mechanism of ADCs.

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4. Bystander killing

Bystander killing is a significant advantage of ADCs that use cleavable linkers. When the cytotoxic payload is released from the ADC molecule, it can diffuse out of the targeted tumor cell and kill neighboring cancer cells, regardless of whether they express the target antigen. This effect can increase the efficacy of the treatment by eliminating a larger area of the tumor. However, bystander killing can also cause damage to healthy cells, leading to unwanted side effects. To achieve bystander killing, the payload molecules must be able to cross the cell membrane. Thus, they should be nonpolar and neutral-charged to penetrate the cell efficiently. The cleavable linker must also be stable enough to retain the payload molecules in the ADC molecule during systemic circulation, but cleavable enough to release them when they reach the target tumor cells.

Antibody-Drug Conjugates in Clinics For Lymphoma.

Table 1. ADCs in clinics target for lymphoma therapies.

ADCs	Antibody	Linker	Payload	Target	indication	Approval Year
Loncastuximab tesirine (Zylonta)	Humanized IgG1	Val-Ala, Cleavable	SG3199 PBD dimer	CD19	diffuse large B-cell lymphoma, high-grade B-cell lymphoma.	20 December 2022, (EMA), 23 April 2023 (FDA)
polatuzumab vedotin (Polivy)	Humanized IgG1	Val–Cit, Cleavable	MMAE	CD79B	Diffuse large B cell lymphoma	16 January 2020 (EMA), 10 June 2019 (FDA)
Brentuximab Vedotin (Adcetris)	Chimeric lgG1	Val–Cit, Cleavable	MMAE	CD30	Relapsed/refractory Hodgkin lymphoma, systemic anaplastic large cell lymphoma	25 October 2012(EMA), 19 August 2011(FDA)

5. Loncastuximab tesirine

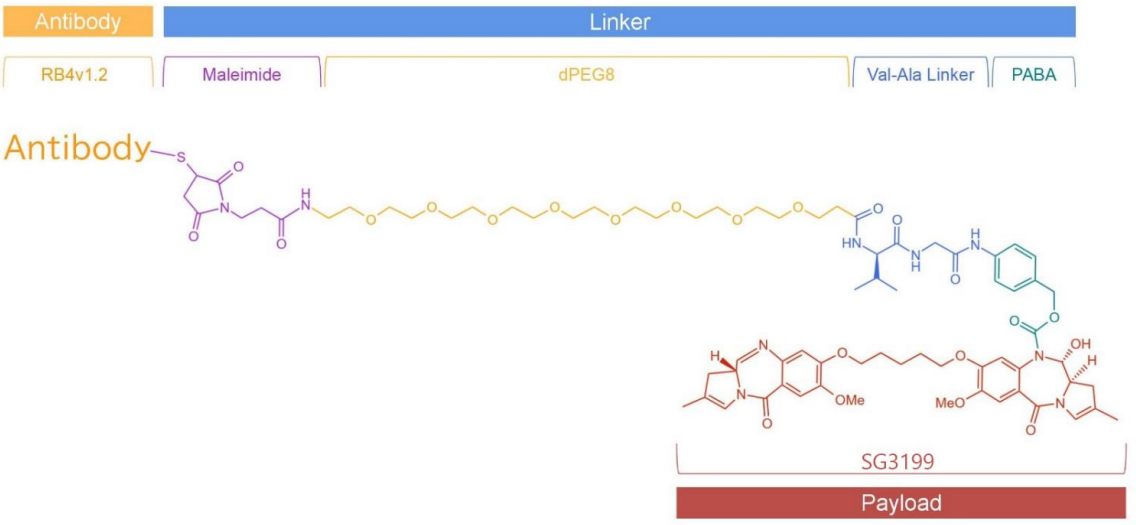

Figure 3. Molecule structure of Loncastuximab tesirine.

Loncastuximab tesirine (Commercial name: Zynlonta) is an ADC for relapsed or refractory large B-cell lymphoma treatment for two or more lines of systemic therapy, including diffuse large B-cell

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lymphoma (DLBCL), but unspecified DLBCL evolved from low-grade lymphoma, and high-grade B-cell lymphoma [19, 20].

Known as the first and only ADC drug targeting CD19.Loncastuximab tesirine is composed of humanized RB4v1.2 mAb, Maleimide, dPEG8, Val-Ala protease-cleavable linker, PABA, and an SG3199 PBD (pyrrolobenzodiazepine) dimer alkylating agent [21]. SG3249 PBD dimer, knowns as Tesirine, SG3199 is the payload released from SG3249 [22]. SG3199 could retain picomolar activity in a panel of cancer cell lines, which is also known as one of the most commonly used and most cytotoxic payloads among ADCs [22]. In April 2021, FDA granted the accelerated approval of Loncastuximab tesirine. The approval is based on data from LOTIS-2, a large (n=145) phase 2 multinational, single-arm clinical study of Zynlonta for the treatment of adult patients with relapsed or refractory DLBCL following two or more prior lines of systemic therapy. Results from the trial demonstrated an overall response rate (ORR) of 48.3% (70/145 patients), which included a complete response (CR) rate of 24.1% and a partial response (PR) rate of 24.1%. Patients had a median time to response of 1.3 months and the median duration of response (mDoR) for the 70 responders was 10.3 months (inclusive of patients who were censored) [23]. However, the safety profile reports a LOTIS-2 study (N=145) with serious adverse reactions occurring in 28% of patients. The most common serious adverse reactions that occurred in ≥2% of patients were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis [24].

6. Polatuzumab vedotin

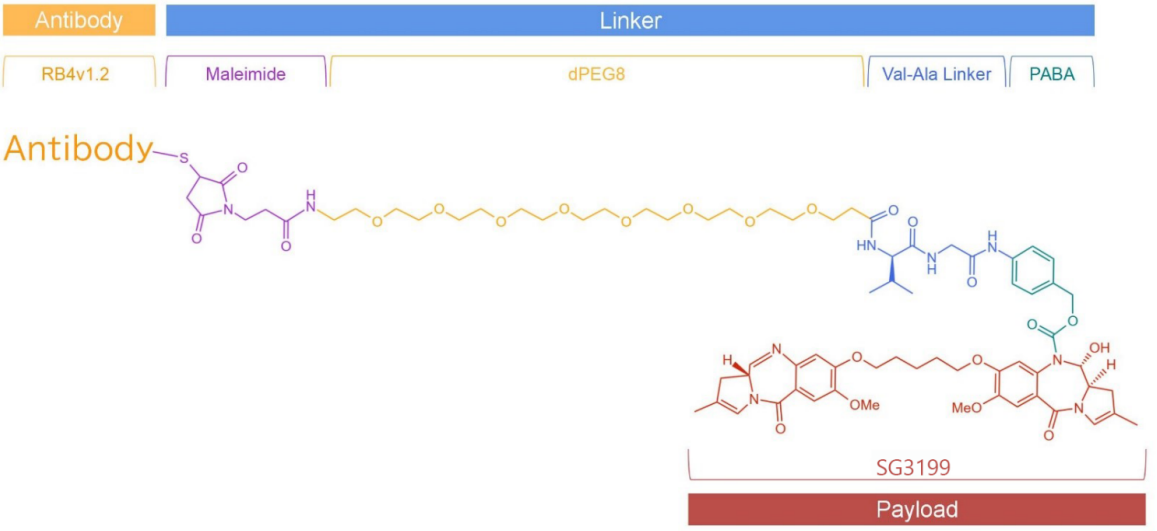

Figure 4. Molecule structure of Polatuzumab vedotin.

Polatuzumab vedotin (Commercial name: Polivy) is an ADC composed of an anti-CD79b mAb linked to tubulin inhibitor MMAE.

Polatuzumab vedotin was granted accelerated FDA approval on June 10, 2019 [25]. Polatuzumab vedotin is usually used to treat adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies with bendamustine and rituximab combined [25]. Polatuzumab vedotin could specifically bind to CD79b and cause the formation of endosomes. Once the lysosome protease cleaves the Linker, MMAE would be released. As one of the most common payloads among ADCs, MMAE could disturb the formation of tubulin polymerization and cause cell apoptosis [25-27[. The appearance of Polatuzumab vedotin also provides an advance in rituximab-cyclophosphamide-hydroxydaunorubicin-Oncovin-prednisone (R-CHOP) in Diffuse large B-cell lymphoma (DLBCL) therapy--polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP), a front-line treatment. A clinical trial

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reveals that the risk of disease progression, relapse, or death is lower among those who received Pola-R-CHP than among those who received R-CHOP [28]. However, the use of Pola-R-CHP is only in its place, notably, in selected patients [29].

7. Brentuximab vedotin

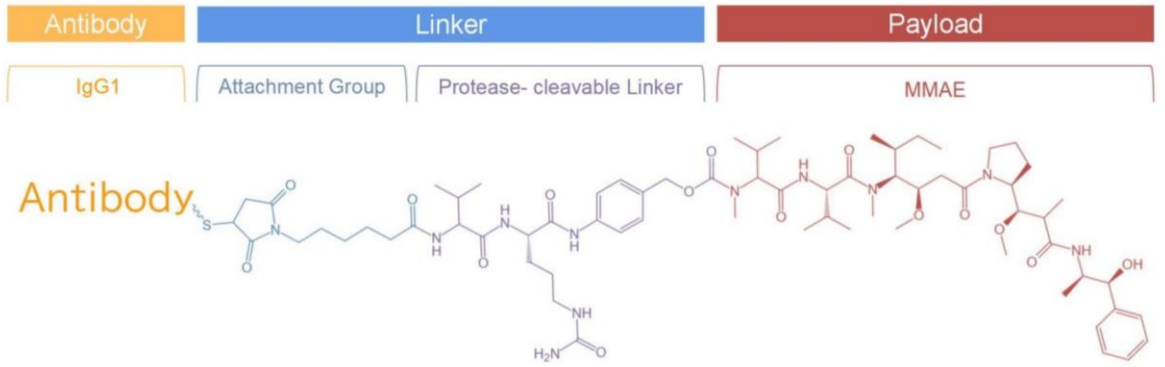

Figure 5. Molecule structure of Brentuximab vedotin.

Brentuximab vedotin (Commercial name: Adcetris) is composed of humanized lgG1 antibody (cAC10), maleimide attachment groups, protease-cleavable linkers, para-aminobenzylcarbamate pacers, and MMAE (payload) [30]. FDA approved Brentuximab vedotin marketing on August 19, 2011 for Hodgkin lymphoma and systemic Anaplastic large cell lymphoma (sALCL) treatment [31]. Brentuximab vedotin is approved for more than 65 countries for relapsed or refractory sALCL or relapsed or refractory classical Hodkin lymphoma therapies [32, 33]. Brentuximab vedotin applied a conditional cleavable valine-citrulline linker to maintain high stability in serum [34].

Through targeting and activating the CD30 on the tumor cells' surface, the brentuximab vedotin will be internalized and transported into the lysosomes, where the proteases cleavage linker will be decomposed into peptide and release MMAE (payload). The payloads released will further interfere with the microtubule construction and polymerization, which will eventually cause cell cycle arrest and apoptosis [35, 36]. The result obtained from first-generation ADCs, shows that only nearly 0.1% of ADC injections could reach their target, which shows the necessity of developing a DAR or potency of the cytotoxicity in the payload of ADC design [37, 38]. Adcetris improved both aspects by utilizing MMAE, a payload with significant cytotoxicity, as its payload. For more, Adcetris increased its DAR to nearly 4, which is significantly larger compared with the first-generation ADCs, like Mylortarg(gemtuzumab ozogamicin) with a DAR of two to three [39]. For patients who have once get treated with Brentuximab vedotin, retreatment of Brentuximab vedotin is often effective [40]. According to an encouraging result of a case series [Bartlett et al. 2010 [41]], Brentuximab vedotin exhibits a significant efficiency in retreatment tolerance. Based on this study, a phase II study about patients who previously experienced an objective response to brentuximab vedotin is ongoing. In March 2018, FDA approved Brentuximab vedotin coadministered in chemotherapy in adult patients who had previously untreated stage III or IV classical Hodgkin lymphoma [42]. Brentuximab vedotin is a treatment before Autologous Hematopoietic Stem Cell Transplantation in Hodgkin lymphoma and also as a consolidation of postautologous transplant in Hodgkin lymphoma [43].

8. Conclusions

As one of the most encouraging cancer therapy developments that ever appeared in human history, ADCs show great potential in overcoming the limitations of conventional therapies. Furthermore, there are tens of kinds of ADCs waiting for marketing approval. Though the current marketing ADCs lack variance toward a specific tumor, with the promising benefit from ADCs' potential market, hundreds of ADCs will be used in cancer therapies within decades.

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However, there are still challenges brought by toxicities from complicated antibody and drug design. Further research and clinical application study is needed. In the near future, the clinical application of ADCs will be generalized, which will lead to the accumulation of more knowledge and boost the design of ADC drugs by scientists. As a result, various kinds of treatment options for cancer patients will be well-developed.

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