Development, efficacy and side effects of antibody-drug conjugates for cancer therapy (Review)

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Abstract. Antibody-drug conjugates (ADCs) are anticancer drugs that combine cytotoxic small-molecule drugs (payloads) with monoclonal antibodies through a chemical linker and that transfer toxic payloads to tumor cells expressing target antigens. All ADCs are based on human IgG. In 2009, the Food and Drug Administration (FDA) approved gemtuzumab ozogamicin as the initial first-generation ADC. Since then, at least 100 ADC-related projects have been initiated, and 14 ADCs are currently being tested in clinical trials. The limited success of gemtuzumab ozogamicin has led to the development of optimization strategies for the next generation of drugs. Subsequently, experts have improved the first-generation ADCs and have developed second-generation ADCs such as ado-trastuzumab emtansine. Second-generation ADCs have higher specific antigen levels, more stable linkers and longer half-lives and show great potential to transform cancer treatment models. Since the first two generations of ADCs have served as a good foundation, the development of ADCs is accelerating, and third-generation ADCs, represented by trastuzumab deruxtecan, are ready for wide application. Third-generation ADCs are characterized by strong pharmacokinetics and high pharmaceutical activity, and their drug-to-antibody ratio mainly ranges from 2 to 4. In the past decade, the research prospects of ADCs have broadened, and an increasing number of specific antigen targets and mechanisms of cytotoxic drug release have been discovered and studied. To date, seven ADCs have been approved by the FDA for lymphoma, and three have been approved to treat breast cancer. The present review explores the function and development of ADCs and their clinical use in cancer treatment.

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1. Introduction

The origin of antibody-drug conjugates (ADCs). Cancer ranks first in mortality worldwide, followed by heart disease (1). Many cancer therapies have been developed, including surgery, chemotherapy, radiotherapy and monoclonal antibodies (mAbs). Although radiotherapy and chemotherapy inhibit tumor growth to help reduce the risk of cancer recurrence, these methods also exert off-target effects and kill nontargeted cells with different degrees of toxicity, and therefore, patients must tolerate an unbalanced immune system (2). The first mAb therapy was developed 40 years ago and was found to attenuate most side effects of traditional treatments. As the forefront of cancer therapeutics with numerous specific agents, mAbs work effectively *in vivo*, protect the host from multisystem damage and promise a long-term disease-free state (3). The concept of mAbs originates from hybridoma cells. These antibodies are produced by B-cell clones that are highly homogeneous and directed against only a specific epitope (4). However, the use of mouse mAbs as therapeutics is restricted by their short half-life, limited effective function and high risk of systemic exposure and toxicity (5). Monoclonal antibody technology was further studied in subsequent decades by combining cytotoxic drugs with antibodies through a chemical linker to decrease toxicity while increasing the efficacy of the payloads and expanding the potential therapeutic window. These new drugs, termed antibody-drug conjugates (ADCs), are biological agents in which a cytotoxic drug is conjugated to a mAb through a linker (6).

ADC components. ADCs include three basic components that are joined through bioconjugation: the antibody, the linker and the payload. Compared with normal cells, ADC target antigens are expressed at remarkably high levels on the surface of tumor cells, which allows the antibodies to effectively bind antigens and cytotoxic drugs to exert their functions. Poor antibody selectivity or the presence of the antigen in normal tissues promotes the delivery of cytotoxic drugs to normal cells, resulting in targeted toxicity. When selecting antigens for ADC development, the following three types of antigens must be distinguished: 1. antigens that are not internalized during antibody binding; 2. antigens that are internalized during antibody binding but are rapidly transferred to the cell membrane; and 3. antigens that are internalized when antibodies are not rapidly transferred. Only the third type of antigen is a valuable target for ADC development (7). Therefore, the appropriate selection of antibodies is particularly important in the development of ADCs (8).

Antibodies As the 'compass' of ADCs, antibody design has attracted considerable attention. Regardless of their investigation in clinical trials or during development, all antibodies in ADCs are human IgG due to their multiple native sites for conjugation and ability to be modified (9). The molecular weight of the antibody should be considered during selection. A high antibody molecular weight slows the diffusion rate, which is not conducive to effective penetration of target cells. Low bioavailability prevents the antibody from penetrating the capillary inner cortex and the extracellular space. However, if the molecular weight of the antibody is too low, its half-life in the body is reduced, which may lead to easy removal (10). Antibodies consist of two dominant fragments: the antigen-binding (Fab) fragment and the crystallizable region (Fc). The Fab is responsible for antigen recognition, and the Fc accepts Fcγ receptors (FcγRI, FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIIA and FcγRIII), which are distributed differently in cells. Differences in the Fc region result in different capacities to bind antigens and activate various effector functions, including antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC). Thus, when selecting a suitable antibody for an ADC, the type of IgG and cellular distribution of the targets should be considered (11). IgG is classified into four subclasses (IgG1, IgG2, IgG3 and IgG4) based on the number of interchain disulfide bonds, the binding affinity of the Fc region and the length of the hinge region (12). Although IgG3 functions best in fixing complement and has the highest binding affinity for FcγRs, this subclass is excluded from use in antitumor therapeutic antibodies due to its short half-life and polymorphic nature, which lead to instability and nonspecific recognition (13). The other subclasses are selected depending on the biological functions and types of target cells.

Linker The linker, which tethers the antibody to the cytotoxic drug via a covalent bond, determines the mechanism and location of payload release. In addition, the linker determines the dose at which drugs act on tumor cells, termed the drug-to-antibody ratio (DAR), which is measured by ultraviolet/visible (UV/VIS) spectroscopic analysis (14). Generally, the DAR is the number of payloads conjugated to the antibody. Three conjugation methods have been developed: i) conjugation with lysine exposed on the surface of the antibody; ii) reduction of cysteine in the interchain disulfide bonds; and iii) site-specific conjugation technologies (including site-specific glycan conjugation, cysteine engineering, incorporation of unnatural amino acids (UAAs) and conjugation of short peptide tags to drug linkers) (15). Among them, lysine conjugation involves many sites, and 0-8 small-molecule toxins can be conjugated to each antibody (i.e., a DAR range of 1-8); therefore, ADC products produced through lysine conjugation in the same batch have high heterogeneity in quality. Cysteine conjugation has relatively controllable conjugation sites because of the fixed positions of the disulfide bonds, but the number of connections is affected by the degree of disulfide bond reduction. When all four interchain disulfide bonds are completely reduced, each antibody can carry eight toxins; when they are partially reduced, products with DARs of 2, 4, 6 and 8 may be generated. Therefore, the cysteine conjugation products have significantly greater homogeneity than the lysine conjugation products. Site-specific conjugation mainly relies on biotechnology to introduce linker sites on the monoclonal antibody, which enables precise site and stoichiometric control. To incorporate UAAs, an orthogonal tRNA/aminoacyl-tRNA synthetase pair is used to replace the amber codon TAG in the monoclonal antibody with p-acetyl phenylalanine (pAcF). Small-molecule toxic drugs are then conjugated to pAcF, and the amount of pAcF represents the amount of drug conjugated (16). With advances in ADC conjugation methods, the problem of heterogeneous DARs in ADCs has been gradually solved. Two broad properties of the linker have been identified, and each retains the homogeneity and stability of ADCs under appropriate conditions (17). The linker is a critical safeguard that maintains the stability of the cytotoxic payload and protects physiological functions by eliminating excess toxicity before internalization. After transport through the blood to localize at tumor sites, removal of the linker accelerates cytotoxic drug release, which is a unique advantage over mAbs (18). Linkers are classified into two groups: cleavable and noncleavable. Cleavable linkers are used more often and have a wider range of applications. In the classical endocytosis pathway, ADCs are delivered into lysosomes, where the cleavable linker can be cleaved by a high concentration of hydrolytic enzymes. Likewise, the cleavable linker responds to acid, reducible disulfides and other exogenous stimuli (19). The noncleavable linker does not actively release payload molecules, and the linker only liberates the payload conjugated to an amino acid residue after the mAb is degraded completely by cytosolic and lysosomal proteases (20).

Payload The payload is essentially a cytotoxic molecule. As an influential factor of ADCs, they are regarded as a 'warhead' that kills target cells (21). Currently, ADC payloads investigated in clinical trials are classified into two categories (antimitotic or DNA damaging) according to their mechanism (22). The main antimitotic payloads include auristatins [monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF)] and maytansinoids [emtansine (DM1), DM3 and DM4], which bind microtubules to inhibit their aggregation, block cell cycle progression and subsequently induce tumor cell apoptosis. The main DNA-damaging payloads include camptothecin analogs (including the exatecan derivative DXd and the irinotecan

metabolite SN-38), which lead to DNA lysis and cell death by binding to the minor groove of the DNA double helix and cause DNA breakage by inhibiting topoisomerase I (TOPO1). Two core characteristics are considered when oncologists select a qualified payload. First, the efficiency of the payload is determined not only by restrictions related to its distribution in tumor tissues and the number of target antigens on the cell surface but also by linker metabolism and the efficiency of internalization and delivery. These limitations can result in the delivery of an insufficient toxin dose to kill tumor cells, and the inherent cytotoxic potency of a payload must be maintained at an extremely high level (23). Finally, the structure of the payload should contain a functional group that is also suitable to bind the antibody. Moreover, the payload must have the ability to dissolve in aqueous solution similar to the intracellular environment and remain stable in plasma to ensure a long antibody half-life.

ADCs in clinical use. ADCs are a promising therapeutic method (24). Since the first ADC was approved by the Food and Drug Administration (FDA) in 2009, at least 100 ADCs have been investigated, and 14 ADCs have been tested in clinical trials (25,26). Although ADCs have faced many clinical failures in the past, advances in humanized monoclonal antibodies, site-specific conjugation protocols, various potent cytotoxic payloads with different mechanisms of action and adaptable linker technologies have improved the properties and alleviated the side effects of previous generations, thereby accelerating the clinical use of ADCs. ADCs have significantly contributed to the future of immuno-oncology by allowing new technologies and biomarker selection strategies (27).

2. First generation of ADCs: Gemtuzumab ozogamicin (GO)

The structure of GO. The monoclonal antibodies used in early ADCs were of murine origin, which led to immune responses and the production of human anti-mouse antibodies (HAMAs). Since the development of GO, a recombinant humanized IgG4 kappa antibody has been used as the antibody in ADCs. GO, also known by the trade name Mylotarg, was the first ADC drug designed for the treatment of acute myeloid leukemia (AML) (28). GO is a recombinant humanized IgG4 kappa antibody that binds to $CD33^+$, which is expressed on the surface of over 90% of blast cells in patients with AML; the antibody is conjugated to the drug via a hydrazone linker (29). The toxic substance (N-acetyl gamma calicheamicin) in GO binds to lysine (Lys) in the head of the antibody through the acid-cleavable linker 4-(4-acetylphenoxy) butanoic acid (AcBut). The average DAR of GO ranges from 2 to 3. When the antibody recognizes CD33, the GO-CD33 complex is internalized, which results in the release of a highly cytotoxic drug (calicheamicin) that causes DNA damage in cells. Calicheamicin induces cytotoxicity by binding to DNA and generating DNA double-strand breaks (30). The binding of GO is followed by internalization of the GO-CD33 complex, after which the highly cytotoxic DNA-strand-breaking calicheamicin compound is released intracellularly, leading to DNA damage and cell death (31).

GO in clinical trials. Initially, GO was indicated for patients aged > 60 years who experienced a first relapse of $CD33^+$ AML and who were not treated with any other ADC and for newly diagnosed patients with AML (aged 18 to 60 years) (32,33). However, GO did not pass the final clinical trials and did not produce a sufficient benefit of longer survival time. In addition, the instability of the linker led to the release of the bound drug within 48 h, and approximately half of the antibodies were unconjugated, which resulted in a high risk of side effects (prolonged thrombocytopenia). The highly hydrophobic nature of calicheamicin, its lack of specificity and its tendency to be eliminated prompted the withdrawal of GO from the commercial market in 2010 (34). Subsequently, oncologists changed to a lower dose and schedule of GO and used it with the traditional chemotherapeutic agents daunorubicin and cytarabine (DA) in 2017 (35). Notably, each medicine has its own dose in different courses (36). In addition to combination therapies, GO can be used as a single agent for patients with $CD33^+$ AML, and different dosages are used for different patient groups. For patients under 2 years old, 3 mg/m^2 is administered on days 1, 4 and 7. Patients with relapsed or refractory disease and patients who have been diagnosed but have not received any treatment receive 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8. If the disease has not progressed, 2 mg/m^2 is injected on the first day of the week every four weeks (37,38). Moreover, patients with higher CD33 positivity are reported to be more sensitive to GO.

Shortcomings of first-generation ADCs. The first-generation ADCs represented by GO have several problems. First, due to insufficient drug efficacy, the drug concentration in the blood is lower than the therapeutically effective concentration, and the low expression of the target antigen leads to limited drug delivery; as a result, the intracellular drug concentration is not sufficient to kill cancer cells. Second, the disulfide bonds in the linkers are easily broken, releasing free ozogamicin into the blood and subsequently causing hepatotoxicity. Third, first-generation ADCs have a weak tumor-targeting effect and a low antigen-binding rate. Fourth, the cytotoxic small molecules in first-generation ADCs are only nonselectively linked to the cysteine or lysine residues of antibodies, and cytotoxin loading is not accurately controlled. Linker instability triggers systemic toxicity, which is the key problem limiting the application of ADCs (39).

3. Second-generation ADCs

Progress achieved in second-generation ADCs. Compared with first-generation ADCs, the greatest advantage of second-generation ADCs is the introduction of a more stable antibody-drug conjugation method and stronger cytotoxicity. For example, brentuximab vedotin has been approved by the FDA to treat $CD30^+$ anaplastic large cell lymphoma and Hodgkin's lymphoma, and its therapeutic effect on cutaneous T-cell lymphoma and peripheral T-cell lymphoma is being verified in phase III clinical trials (40,41). Brentuximab vedotin carries the antimitotic agent MMAE and is linked to IgG1 through the protease cleavable linker Val-Cit (42,43). Inotuzumab ozogamicin is also used to treat lymphoma, and although it initially targeted patients with $CD22^+$ ALL, it was

later confirmed to have the potential to treat non-Hodgkin's lymphoma and Hodgkin's lymphoma (44). Inotuzumab ozogamicin consists of an acid-cleavable linker coupling an IgG4 monoclonal antibody and a calicheamicin derivative. Next, this article introduces a representative second-generation ADC, ado-trastuzumab emtansine (T-DM1), in detail.

The structure of T-DM1. Breast cancer (BC) is a dominant malignant disease that results in the death of women worldwide (45). Some patients with BC (15-30%) exhibit overexpression of the HER2 human epidermal growth factor receptor, which is associated with disease development (46,47). T-DM1 was a second-generation ADC that was developed for HER2-positive patients and included the monoclonal antibody trastuzumab, which was initially approved in 2013 (48). The previous generation was hampered by numerous pharmacological and safety considerations, but in contrast, T-DM1 shows better cell-mediated cytotoxicity and greater affinity for tumor cells, which may reduce irrelevant damage to healthy cells (49). The antibody of this ADC is IgG1, which carries the antimitotic maytansinoid DM1 as the payload. DM1 is a derivative of maytansine, which controls cellular division by potently inhibiting tubulin polymerization, resulting in apoptosis (50). The antibody and payload are bound by a noncleavable linker, N-succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate, and a DAR of 3.5 has been confirmed (51).

T-DM1 in clinical trials and side effects. The approval of T-DM1 by the FDA/European Medicines Agency (EMA) as a second-line treatment for HER2-positive breast cancer was based principally on three pivotal phase III trials-EMILIA, TH3RESA and MARIANNE (52). In the EMILIA trial, T-DM1 was superior to the traditional chemotherapy regimen tested (capecitabine plus lapatinib) in terms of progression-free survival (PFS; 9.6 vs. 6.4 months) and overall survival (OS; 30.9 vs. 25.1 months) (53). Patients in the T-DM1 arm also showed a higher response rate (43.6% vs. 30.8%; P<0.001) and fewer grade 3-4 adverse events (AEs) (41% vs. 57%). Other indices, such as quality of life (QoL), confidence interval (CI) and duration of response (DoR), were improved with T-DM1 treatment (54). In the TH3RESA trial, the patients were divided into groups receiving T-DM1 or physician's choice (PC). Similar to the EMILIA trial, OS and PFS were significantly improved in patients treated with T-DM1, and the pharmacokinetics of T-DM1 in the TH3RESA trial suggested that patients treated with a dosage of 3.6 mg/kg T-DM1 every 3 weeks experienced a benefit compared with PC (55). These two clinical trials shifted T-DM1 to a second-line treatment choice (56). In the MARIANNE trial, patients with HER2-positive metastatic breast cancer (MBC) who were not previously treated were randomized to receive T-DM1 plus placebo or pertuzumab and a trastuzumab-taxane combination. To compare T-DM1 (with or without pertuzumab) with trastuzumab plus taxane, subgroups were tested for the following biomarkers: HER2 and HER3 mRNA expression levels; HER2 staining intensity; phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) status; phosphatase and tensin homolog (PTEN) H-score; and PTEN protein expression level (57). However, no significant differences were observed between these two groups in the levels of biomarkers related to the HER2 pathway. In conclusion, the median OS was similar across groups, and T-DM1 remains reserved as a second-line treatment because its actual efficacy is unclear (58). One of the most important side effects observed during the course of T-DM1 treatment is thrombocytopenia, which can lead to a reduction in drug dosage and even withdrawal (59). The guideline recommends that T-DM1 be suspended until a platelet (PLT) count $\geq 75{,}000/mm^3$ is observed, at least for patients with grade 3 thrombocytopenia, while the dosage should be less than the previous dosage after the PLT count recovers for patients with grade 4 thrombocytopenia (PLT $<25{,}000/mm^3$) (60). This adverse reaction results from Fc receptor engagement, which inhibits megakaryocyte differentiation because of internalization by a macropinocytosis pathway independent of FcγRIIA therapeutics (61).

4. Third-generation ADCs

Progress achieved in third-generation ADCs. In the past decade, the experience obtained with first- and second-generation ADCs has paved the way for the development of third-generation ADCs. Third-generation ADCs utilize the site-specific binding of small-molecule drugs to monoclonal antibodies, which improves the stability and pharmacokinetics and increases the drug release rate without causing additional systemic toxicity or producing unbound monoclonal antibodies. Compared with second-generation ADCs, third-generation ADCs have more optimized linkers and conjugation mechanisms and thus a wider therapeutic window. The use of site-specific conjugation ensures the reproducibility of the DAR and efficacy of third-generation ADCs, improves their therapeutic index and maximizes their killing effect on tumor cells with low target expression. Polatuzumab vedotin targets CD79b and has been used to treat diffuse large B-cell lymphoma. This ADC is formed by linking the cleavable linker Val-Cit to IgG1 and MMAE mAb (62). Sacituzumab govitecan is an anti-trophoblast cell-surface antigen 2 (anti-Trop-2) ADC linked to the topoisomerase inhibitor SN-38 through a proprietary hydrolyzable linker. This ADC is used for the treatment of triple-negative breast cancer (TNBC). Although its DAR is as high as 7.6, its tolerance and efficiency are also high (63). In addition, enfortumab vedotin, which targets nectin-4, is used to treat refractory metastatic urothelial cancer (64). Belantamab mafodotin, which targets BCMA, is used to treat relapsed or refractory multiple myeloma (RRMM) (65). Table I summarizes three generations of ADCs which have been approved by FDA for treating cancers. Next, this review will introduce a representative third-generation ADC, trastuzumab deruxtecan (T-DXd/DS8201), in detail.

The structure of T-DXd/DS8201. In 2020, T-DXd was approved and became the second ADC for $HER2^+$ therapy (66). Similar to T-DM1, T-DXd was also designed for HER2-positive patients. T-DXd consists of an anti-HER2 humanized monoclonal IgG1 (MAAL-9001) with the same amino acid sequence as trastuzumab. Unlike T-DM1, which carries DM1, T-DXd is conjugated to seven or eight molecules of an exatecan derivative, DXd (topoisomerase I inhibitor), per molecule of the anti-HER2 monoclonal antibody through a novel linker-payload system (67). In addition to payload, T-DXd is superior to T-DM1 in many ways, including possessing a

Table I. Approved antibody-drug conjugates for clinical use by U.S Food and Drug Association (17).

Generation	Antibody-drug conjugate	Target antigens	Linker type	Payload	Indication
First generation	Gemtuzumab ozogamicin	CD33	The cleavable linker, 4-(4-acetylphenoxy) butanoic acid (acbut)	Calicheamicin	Acute myeloid leukemia
Second generation	Brentuximab vedotin	CD30	The cleavable linker, Val-Cit	MMAE	Relapsed Hodgkin lymphoma and systemic, anaplastic large cell lymphoma
Second generation	Inotuzumab ozogamicin	CD22	The cleavable linker, acbut	Calicheamicin	Acute lymphoblastic leukemia
Second generation	Ado-trastuzumab emtansine	HER2	The non-cleavable linker, N-succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate	DM1	$HER2^+$ Breast cancer
Third generation	Polatuzumab vedotin	CD79b	The cleavable linker, Val-Cit	MMAE	Large B-cell lymphoma
Third generation	Sacituzumab govitecan	TROP-2	The cleavable linker, CL2A	SN-38	Triple-negative breastcancer
Third generation	Enfortumab vedotin	NECTIN-4	The cleavable linker, Val-Cit	MMAE	Metastatic urothelial cancer
Third generation	Belantamab mafodotin	BCMA	The non-cleavable linker, MC	MMAF	Relapsed or refractory multiple myeloma
Third generation	Trastuzumab deruxtecan	HER2	The cleavable linker, tetrapeptide	DXd	$HER2^+$ breast cancer
Third generation	Vadastuximab talirine	CD33	The cleavable linker, Val-Cit	PBD dimer	Acute myeloid leukemia

short half-life and a wider therapeutic window; in addition, neither T-DXd nor T-DM1 increases the cytotoxic effect, and they do not expose normal cells to the drug through off-target toxicity (68). Moreover, T-DXd provides a new capability, the 'bystander killing effect', as it kills tumor cells in close proximity to the targeted cells by releasing deruxtecan into intercellular spaces to attack neighboring tumor cells, regardless of the HER2 expression level (69).

T-DXd in clinical trials and side effects. Three phase III clinical trials are ongoing (NCT03523585, NCT03529110 and NCT03734029) (70). The first two studies reported that T-DXd is most effective for patients with HER2+ BC who were either treated with the combination of a mAb (trastuzumab) and traditional chemotherapy or with a mAb (trastuzumab) and a taxane, followed by T-DM1 (71). T-DXd has also been applied to treat HER2-low MBC, an indication that was identified in the third trial (72,73). Another trial further revealed that T-DXd is effective in patients with MBC with low HER2 expression. In this clinical trial, patients with low HER2 expression were randomly divided into two groups that received T-DXd or the PC of chemotherapy. Patients in the T-DXd arm experienced significantly longer PFS and OS than those who received the PC of chemotherapy. Furthermore, another study determined a recommended dose by evaluating the efficacy and safety of different doses of T-DXd (74). Exposure-efficacy modeling showed better exposure and response rates and longer PFS after treatment with a higher dose (71). Additionally, key AEs, including interstitial lung disease, nausea and myelosuppression, were also related to treatment with a higher dose. To achieve a balance between safety and efficacy, and after the optimal dose was calculated, 5.4 mg per kilogram was recommended (75). In addition to BC, T-DXd is efficacious against gastric cancers that express HER2. T-DXd has already been approved by the FDA and is recommended in the Japanese Gastric Cancer Association treatment guidelines as the third-line treatment for HER2-positive gastric cancer (76). The trial method was similar to that for BC, and the primary outcome was the objective response, which was criticized by the independent central review. Some indices, including OS, DoR, PFS, confirmed response (response persisting ≥4 weeks) and safety, were also considered (77). Compared with standard therapies, T-DXd therapy resulted in significant improvements in response and OS. Apart from BC and gastric cancer, ongoing clinical trials are being conducted to determine the efficacy of T-DXd alone or in combination against other solid tumors, such as HER2-expressing colorectal cancer and HER2-expressing or HER2-mutated non-small cell lung cancer (NSCLC), for which the FDA has granted accelerated approval (78). The limited outcomes revealed that T-DXd has promising anti-

tumor activity with an acceptable safety profile in patients with HER2-expressing or HER2-mutant solid tumors who have received extensive pretreatment, especially patients with HER2-mutant NSCLC (79). In addition to NSCLC, T-DXd also showed preliminary activity against HER2-expressing colorectal cancer[9]. In the clinical trial, all patients injected with 5.4 mg/kg experienced at least one AE to different extents during treatment. In addition to some common AEs, such as nausea and myelosuppression, some severe AEs including hematological and pulmonary diseases [e.g., diffuse parenchymal lung disease (DPLD)] are common (80). A study in monkeys explored the relationship between dose and DPLD severity. Since the histopathological features in the monkeys were similar to those of DPLD associated with anticancer drugs in patients, the results from this study are translatable to humans. In conclusion, the risk of T-DXd-induced AEs depends on both a higher dose and the dosing frequency (81). Physicians should confirm that patients do not have pulmonary diseases, irrespective of the grade, and appropriate measures should be implemented before prescribing T-DXd to avoid fatal AEs (82).

5. Conclusions and future perspectives

Since a single medication, regardless of whether it is standardized chemotherapy or mAb treatment, may exert off-target effects, the use of ADCs in clinical cancer treatment has gradually become a mainstream method. After decades of research and clinical trials, ADCs have been updated to the third generation through optimization of intrinsic activity parameters and development of mAbs and linkers. The previous conjugation methods and selection of cytotoxic drugs have been improved, while the selection of the composition and mode of component binding are gradually becoming more mature through further exploration. The payload is released in the plasma where it remains stable and highly effective. In addition, the dose of cytotoxin that reaches the tumor site may be controlled by novel linkers.

However, further development of third-generation ADCs can still occur, and researchers are focused on the development of targets with dual-specificity and on drugs that carry two different payloads. The former refers to the design of an ADC that targets two different sites on one antigen to accelerate lysosomal aggregation and load delivery. The latter refers to ADCs that carry two drugs; by accurately controlling the ratio of the two drugs, the payload can be delivered synergistically and effectively to cancer cells to reduce the rate of drug resistance. In addition to improving the ADC release mechanism, oncologists are also seeking to identify additional biomarkers. The accurate identification of biomarkers improves the immunogenicity of targeted cells, increases tumor specificity and protects normal cells from attack, which enables ADCs to have higher efficacy in cancer treatment. Finally, optimizing the dosage and reducing drug side effects and drug resistance, which are also ultimate challenges that must be overcome for these drugs to be used in the clinic, are crucial to ensure the safety and wide application of ADCs. In addition to their use as single agents, the combination of ADCs with monoclonal antibodies or chemotherapeutic drugs has also attracted substantial attention. Combination medications may reduce the risk of hematologic and pulmonary diseases and liver damage resulting from ADCs. If ADCs bind tumors and their pharmacological activity is maximized, the therapeutic effects on tumors will be substantially enhanced.

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Authors' contributions

TS and RQ conceived and designed the study. TS wrote the first manuscript. XN, QH, ML, SQ and RQ revised the content and grammar of the manuscript. RQ, ML and SQ provided guidance and correction. ML, RQ and SQ acquired funding. All authors have read and agreed to the published version of the manuscript. Data sharing is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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