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Antibody-drug conjugates in HER2-positive breast cancer

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Abstract

Antibody-drug conjugates (ADCs) combine the high specificity of monoclonal antibodies with the high anti-tumor activity of small molecular cytotoxic payloads. The anti-tumor activity of ADCs is mainly achieved by the direct blocking of the receptor by monoclonal antibodies, direct action and bystander effect of cytotoxic drugs, and antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. ADCs have been used in adjuvant therapy and rescue treatment of human epidermal receptor 2 (HER2)-positive breast cancer, greatly improving the prognosis of breast cancer patients. Several ongoing clinical trials of ADC for breast cancer and other solid tumors proved the potential of ADCs will provide more promising treatment options for patients with malignant tumors. This review introduces the mechanism and latest clinical progress of ADC drugs approved for HER2-positive breast cancer to guide clinical practice and conduct research.

Keywords: Antibody-drug conjugate; HER2-positive; Breast cancer; T-DM1; DS-8201

An antibody-drug conjugate (ADC) is composed of a monoclonal antibody linked to a small molecular cytotoxic payload through a cleavable or non-cleavable linker. With the approval of trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (DS-8201a),[1,2] ADC has created a new era of targeted therapy for breast cancer. However, the development process of ADCs is relatively tortuous. It took over 100 years from the proposal of the ADC design concept to the approval of the first drug for marketing.[3] This article summarizes the mechanism of ADC in human epidermal receptor 2 (HER2)-positive breast cancer therapy, as well as the latest clinical trial progress and common adverse effects (AEs) of approved ADCs.

Composition and Mechanism of ADCs

ADC combines the targeting specificity of monoclonal antibodies with the high toxicity of cytotoxic drugs. However, the anti-tumor mechanism of ADCs is complex, and any component may affect their efficacy and AEs. Several reviews have been published on the components and mechanisms of action of ADC.[4,5] This part of the content focuses on the properties of different components and pharmacokinetic parameters of T-DM1 and DS-8201a.

Target antigen and monoclonal antibody

The targeted antigen should be highly expressed in tumor tissues, but not expressed or expressed at low levels in normal tissues to facilitate highly specific binding with monoclonal antibodies and deliver an effective active dose of the payload to the tumor tissues. Currently, the approved agents for breast cancer target HER2 and human trophoblast cell-surface antigen 2 (TROP2), respectively. Among them, HER2 is overexpressed and amplified in 15% to 20% of breast cancers,[6] and TROP2 is overexpressed in various epithelial neoplasms, especially in triple-negative breast cancer.[7] Most clinical trials on other target antigens, such as epidermal growth factor receptor and Notch3, are still in phases I and II.[8,9] All ADCs currently approved for breast cancer use humanized immunoglobulin G (IgG) 1 as a monoclonal antibody.[10,11]

Linker

The linker conjugates the payload with the monoclonal antibody, which is a key factor in delivering a payload to tumor cells. It must have good stability in the blood circulation. An unstable linker releases the payload earlier, which reduces the efficacy and increases the off-target toxicity. Depending on whether the linker is lysed in the cell, it can be classified as cleavable and non-cleavable.

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ADCs with different types of linkers have different anti-tumor mechanisms, which will be discussed below.

Payload

The most commonly used payloads in ADCs are tubulin inhibitors and topoisomerase inhibitors. The number of antigens on the tumor cell surface is small, and the number of small-molecule cytotoxic payloads that ADCs can carry is limited. To achieve an effective therapeutic concentration, it is necessary to choose cytotoxic drugs with a low half-maximal inhibitory concentration (IC50). The damage to normal tissues is correspondingly reduced owing to the precise targeting of monoclonal antibodies. The number of small-molecule cytotoxic drugs conjugated to each antibody, also known as the drug-to-antibody ratio (DAR), is an important parameter for evaluating the efficacy and toxicity of ADCs. The currently recommended DAR range is 2 to 4, with an emphasis on uniformity. With an increase in DAR, the plasma clearance rate of the ADC is increased, and the half-life is shortened.

Mechanism of ADCs

The main anti-tumor mechanism of ADCs targeting HER2 is shown in Figure 1. The monoclonal antibody in the ADCs serves as a carrier to transport payloads to target tumor cells. Trastuzumab in ADCs binds to the extracellular domain IV of HER2 and inhibits HER2 homodimerization, thereby blocking HER2-mediated signaling pathways.[12] ADCs with the cleavable linkers directly release the payloads in the tumor microenvironment or in the target cell, whereas ADCs with non-cleavable linkers enter the tumor cell and are degraded in the lysosome to release the payloads. The highly membrane-permeable payloads can penetrate the cell membrane to kill adjacent HER2-negative tumor cells, known as the bystander effect, which can further improve the efficacy in heterogeneous tumors. Non-cleavable linkers provide greater stability and therapeutic efficacy, whereas cleavable linkers usually have a bystander effect. In addition, ADCs can inhibit the shedding of the extracellular domain of HER2 and induce tumor cell apoptosis through cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [Figure 1].[13]

Comparison of features and pharmacokinetic parameters between T-DM1 and DS-8201a

Table 1 shows the comparison between T-DM1 and DS-8201a in terms of their features and pharmacokinetic parameters, which will affect the drug dosage, efficacy, and toxicity. Both DS-8201a and T-DM1 use IgG1 as a monoclonal antibody. Gemtuzumab ozogamicin and inotuzumab ozogamicin, which have been approved for hematological malignancies, use recombinant humanized IgG4 antibodies, and some ADCs in clinical trials use humanized IgG2 antibodies, such as glembatumumab vedotin and AGS-16C3F. Compared with IgG2 and IgG4, IgG1 and IgG3 can induce stronger ADCC and CDC.[14] However, IgG3 is not recommended because of its long-hinged region and polymorphic properties, which increase
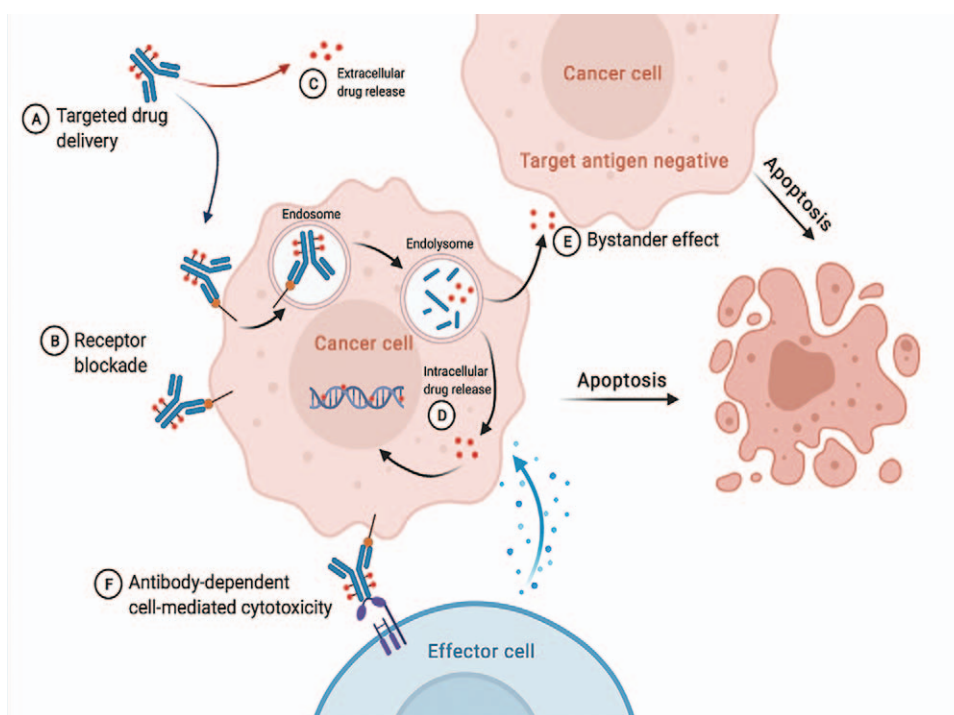

Figure 1: The main mechanism of ADCs targeting HER2. A: The monoclonal antibody in the ADCs serves as a carrier to transport payloads to target tumor cells. B: Trastuzumab in ADCs binds to the extracellular domain IV of HER2 and inhibits HER2 homodimerization. C: ADCs with the cleavable linkers directly release the payloads in the tumor microenvironment or in the target cell. D: ADCs with non-cleavable linkers enter the tumor cell and are degraded in the lysosome to release the payloads. E: The highly membrane-permeable payloads can penetrate the cell membrane to kill adjacent HER2-negative tumor cells, known as the bystander effect. F: ADCs can inhibit the shedding of the extracellular domain of HER2 and induce tumor cell apoptosis through cell-mediated cytotoxicity (ADCC). ADCs: Antibody-drug conjugates; HER2: Human epidermal receptor 2.

Table 1: Comparison of features and pharmacokinetic parameters between T-DM1 and DS-8201a.

Parameter	Trastuzumab emtansine	Trastuzumab deruxtecan
Alternative names	T-DM1	DS-8201a
Trade name	Kadcyla	Enhertu
Target (antibody)	HER2 (trastuzumab)	HER2 (trastuzumab)
Antibody type	Humanized IgG1	Humanized IgG1
Payload	DM1 (derivative of maytansine)	DXd (derivative of DX-8951)
Mechanism of payload	Tubulin polymerization inhibitor	Topoisomerase I inhibitor
Bystander effect	No	Yes
Linker	Thioether SMCC linker	Maleimide tetrapeptide linker
Linker type	Uncleavable	Cleavable (protease)
DAR	3.5	8
Year of initial approval	2013	2019
Approved indication(s)	HER2-positive mBC and HER2-positive EBC with invasive residual disease	HER2-positive mBC
Standard dosage	3.6 mg/kg, every 3 weeks	5.4 mg/kg, every 3 weeks
Pharmacodynamics		
IC50 (ng/mL)	11–112	6.7–26.8
Pharmacokinetics		
C_{max} (µg/mL)	76.2 ± 19.1	127 ± 17.2
t_{max} (h)	0.5	1.9
AUC_{inf} (µg · day^{-1} · mL^{-1})	300 ± 66	590 ± 186
Vd_{ss} (mL/kg)	58.4 ± 12.4	75.2 ± 24.2
t1/2 (days)	3.1 ± 0.7	6.03 ± 0.60
Clearance (mL · day^{-1} · kg^{-1})	2.7 ± 3.6	10.1 ± 3.90

AUC_{inf}: Area under the concentration-time curve from 0 to infinity; C_{max}: Maximum observed plasma concentration; DAR: Drug-to-antibody ratio; EBC: Early-stage breast cancer; HER2-positive: Human epidermal receptor 2 positive; IgG: Immunoglobulin G; IC50: Inhibitory concentration; mBC: Metastatic breast cancer; SMCC: Succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate; t_{max}: Time of occurrence of the maximum concentration; t1/2: Elimination half-life.

its instability and immunogenicity.[15] Therefore, IgG1 antibodies, such as trastuzumab, are the best choice for ADCs targeting HER2.

The average DAR of T-DM1 is 3.5, which is also within the recommended DAR range, whereas DS-8201A has a high DAR of 8. Under the premise of controlled safety, ADCs with a higher DAR can deliver more payloads, thus showing better efficacy. Strikingly, the IC50 of payloads in T-DM1 and DS-8201a was higher than that of conventional chemotherapeutic agents.[16,17] However, the anti-tumor mechanisms of payloads in DS-8201a and T-DM1 are different. The former is a topoisomerase I inhibitor, whereas the latter is a tubulin polymerization inhibitor. Moreover, DS-8201a has a highly membrane-permeable payload and kills adjacent HER2-negative tumor cells through the bystander effect.

New advances in clinical research

Recently, the 5-year survival rate of breast cancer has reached 80%.[18] With the improvement in the overall survival (OS) of breast cancer, drug resistance has become a great challenge. ADCs are among the most promising drugs for treating tumors. The approval of DS-8201a and T-DM1 improved the prognosis of HER2-positive breast cancer.

ADCs in advanced HER2-positive breast cancer

ADCs revised the treatment guidelines for HER2-positive breast cancer and provided patients with promising treatment options. Compared with capecitabine plus lapatinib, T-DM1 significantly improved the median progression-free survival (PFS) (6.4 months vs. 9.6 months), and median OS (25.1 months vs. 30.9 months) in the phase III EMILIA study.[19] Based on the results of the EMILIA study, T-DM1 was approved by the Food and Drug Administration in 2013 for the treatment of patients with HER2-positive metastatic breast cancer (mBC) who previously received trastuzumab and taxane, separately or in combination.[1] TH3RESA further confirmed the efficacy and safety of T-DM1 in HER2-positive advanced breast cancer.[20]

DESTINY-Breast01 aimed to evaluate the safety and efficacy of DS-8201a in HER2-positive advanced breast cancer patients who previously received T-DM1.[21] The median number of previous lines of therapy for metastatic disease was 6, suggesting that the enrolled patients were severely resistant to anti-HER2 therapy. The results showed that the objective response rate (ORR) reached 60.9%, of which 6.0% were complete responses and 54.9% were partial responses.[21] Therefore, DS-8201a is significantly superior to other anti-HER2 therapies. It was approved in 2019 for the treatment of adult patients with HER2-positive, unresectable, or mBC who had received two or more anti-HER2 therapies.

The European Society for Medical Oncology Congress 2021 and American Society of Clinical Oncology Annual Meeting 2021 also announced the progress of ADCs in HER2-positive breast cancer. The results of the

phase III DESTINY-Breast03 study showed that DS-8201a had better PFS and ORR than T-DM1 in patients previously treated with trastuzumab and taxane whereas the rates of adverse events were similar.[22] In the phase I study of ARX788, the ORR of the 1.5 mg/kg dose group reached 74%, and the disease control rate reached 100%.[23] It has obtained the fast-track qualification granted by the Food and Drug Administration. A166 is an ADC composed of a novel cytotoxic drug (Duo-5, anti-microtubule agent) and trastuzumab.[24] In the phase I study of A166, the ORR of the 6 mg/kg dose group also reached 59.1%.[24] The application of ADCs in HER2-positive breast cancer will become more and more common.

ADCs in adjuvant and neoadjuvant therapy

As the first optimized treatment study for residual lesions after neoadjuvant treatment of HER2-positive breast cancer, the KATHERINE study achieved breakthrough results. Compared with trastuzumab, T-DM1 treatment significantly improved the invasive disease-free survival (88.3% *vs.* 77.0%), with an absolute value benefit of 11.3%.[25] However, it is still unclear whether patients who have not received neoadjuvant therapy can benefit from T-DM1 adjuvant therapy.[26,27] Dual HER2-targeted neoadjuvant therapy with pertuzumab plus trastuzumab significantly reduced the risk of HER2-positive breast cancer recurrence. The efficacy and safety of neoadjuvant T-DM1 plus pertuzumab were also assessed in the phase III KRISTINE study but did not reach the primary clinical endpoint.[28] There have been no clinical studies of DS-8201a exploring adjuvant and neoadjuvant therapy in breast cancer, but due to its high incidence rate of serious AEs, caution should be taken while conducting clinical trials.

ADCs in HER2 low-expressing breast cancer

Monoclonal antibodies are only effective for HER2-positive (immunohistochemistry [IHC] 3+ or 2+ with fluorescence *in situ* hybridization [FISH] amplification) breast cancers and do not exert significant anti-tumor activity against low-expression HER2 (IHC1+ or IHC2+/FISH negative) breast cancers.[29] In fact, only 15% to 20% of breast cancers are HER2-positive, and most breast cancers have low HER2 expression.[30] Furthermore, several studies have confirmed that HER2 amplification is lost or downregulated in metastatic tumors.[31,32] DS-8201a showed satisfactory efficacy in patients with HER2 low-expressing mBC.[21,33] The ORR of DS-8201a in HER2 low-expressing breast cancer reached 37%, and the median PFS was 11.1 months.[33] There have been no prospective clinical studies on T-DM1 in breast cancer with low HER2 expression, but exploratory analyses have shown limited efficacy.[34] Novel ADCs, such as trastuzumab duocarmazine and ARX788, have also shown potential anti-tumor activity against breast cancer with low HER2 expression in preclinical models or clinical trials.[35,36] This suggests that there may be a need to redefine HER2-positive breast cancer and identify optimal candidates who would benefit from anti-HER2 therapy.

ADCs in HER2-positive breast cancer with brain metastases (BMs)

Most chemotherapeutic and targeted agents have difficulty passing through the blood–brain barrier; therefore, patients with BMs tend to have a poor prognosis. Patients with HER2-positive breast cancer have the most frequent BMs.[37] As a novel anti-HER2 ADC, T-DM1 exhibits favorable efficacy in patients with BMs. In the BMs subgroup of the EMILIA study, the median OS of T-DM1 was more than twice that of lapatinib plus capecitabine (26.8 months *vs.* 12.9 months).[38] Montemurro et al[39] analyzed 126 patients with measurable BMs in the KAMILLA study. The results showed that 67% of patients had target lesion reduction, and the clinical benefit rate reached 43%. Moreover, the median PFS was 18.1 months among the 24 patients with asymptomatic BMs in the DESTINY-Breast01 study.[21] The efficacy of the secondary prevention effect of T-DM1 combined with temozolomide rhythm chemotherapy on locally treated HER2-positive breast cancer with BMs was evaluated in a phase I/II study.[40]

ADCs combined with other treatments

NSABP FB-10 initially explored the efficacy of T-DM1 plus lenvatinib in patients with disease progression after previous trastuzumab plus pertuzumab treatment, with an ORR of 63%.[41] The combination of ADC with other targeted therapies and the combination of ADC with bispecial-specific antibodies is worthy of further exploration.[42,43]

T-DM1 combined immunotherapy has shown promising efficacy against breast cancer. ADCs can mediate ADCC, induce lymphocyte infiltration in the tumor microenvironment, upregulate the expression of immune checkpoint receptors of CTLA4, PD-1, and PD-L1, and enhance the immune response.[44] Phase II of the KATE2 study compared the efficacy and safety of T-DM1 plus atezolizumab with T-DM1 monotherapy for trastuzumab- and taxane-treated HER2-positive advanced breast cancer.[45] There were no significant benefits from PFS in the intention to treat the population. However, in the PD-L1 positive subgroup, the median PFS (8.5 months *vs.* 4.1 months) and 1-year OS rate (94.3% *vs.* 87.9%) of T-DM1 plus atezolizumab were significantly improved. For HER2 and PD-L1 "double positive" patients, targeted therapy combined with immunotherapy was hopeful to further improve the prognosis.

The WSG ADAPT study explored the efficacy of T-DM1 combined with endocrine therapy in neoadjuvant therapy. The pathological complete response rate of the two regimens containing T-DM1 was >40%, while that of the trastuzumab regimen was 15% (*P* < 0.001).[26] T-DM1 combined with endocrine therapy is expected to replace targeted therapy combined with chemotherapy in the future, as well as become a new adjuvant treatment option for HER2-positive and hormone receptor (HR)-positive breast cancer. The study also suggested that early breast cancer patients who are both HER2- and HR-positive have unique biological characteristics, and future

Figure 2: Incidence of adverse events with DS-8201a and T-DM1. (A) Incidence of any grade adverse events with DS-8201a and T-DM1. (B) Incidence of grade 3–5 adverse events with DS-8201a and T-DM1.

studies should evaluate the efficacy of patients with different HR statuses separately.

Adverse Events of ADCs Approved in HER2-Positive Breast Cancer

The toxicity of ADCs can be caused by multiple mechanisms, including monoclonal antibodies, payloads, off-target effects, ADCC, and CDC. Therefore, the AEs of ADCs are diverse [Figure 2], and clinicians should pay close attention to their toxicity. The most common AEs were nausea, fatigue, alopecia, and thrombocytopenia.[21,46] The most commonly reported grade 3–5 AEs with T-DM1 were thrombocytopenia, anemia, and elevated serum concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT)[46]. Compared with T-DM1, DS-8201a had a higher frequency of grade 3 or higher AEs (52.2% *vs.* 47.6%). Grade 3 or 4 increased AST or ALT with DS-8201a was relatively rare, but hematologic toxicity (except thrombocytopenia), such as neutropenia, anemia, and leukopenia, was more serious.[21] Thrombocytopenia is a special AE of T-DM1, and the incidence of any grade events was 8.7% to 30.6% (incidence of grade 3–5 events is 2.7%–14.0%).[46,47] Compared with DS-8201a, peripheral neuropathy caused by T-DM1 was more serious.[46] Most AEs were grade 1 or 2 and did not require dose reduction or discontinuation of therapy. Approximately 10% to 15% of all patients discontinued therapy due to AEs.[19,21,34] Notably, the AEs related to the discontinuation of DS-8201a were mainly due to pneumonitis and interstitial lung disease.[21,48]

Conclusions

Till August 30, 2021, there have been >1000 clinical trials on ADCs registered on the website (https://clinicaltrials. gov). The excellent efficacy and controllable safety of T-DM1 and DS-8201a in HER2-positive breast cancer have been confirmed, but ADCs, such as A166, RC48, and ARX788, are still in phase I or II clinical trials.[36,49,50] Relevant studies on predicting efficacy, drug resistance biomarkers, and other evaluation methods are also actively carried out,[51-54] which will further promote and optimize the clinical application of ADCs. Additionally, clinical trials of ADC in other malignant solid tumors, such as lung cancer and gastric cancer, are also ongoing.[55,56] The potential anti-tumor activity of ADC will provide more promising treatment options for patients with malignant tumors in the future.

Funding

Conflicts of interest

None.

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