Clinical Toxicity Of Antibody Drug Conjugates

Antibody–drug conjugates (ADCs) have made considerable progress in 10 years. Several ADCs are ranked among the first-line therapies, providing significant clinical benefits to oncology patients. **However, their side effects should not be ignored.** Interstitial lung disease, hematologic toxicity, hepatic and renal toxicity, and black box warnings continue to limit the clinical performance of ADCs to some extent. Therefore, the use of ADC requires careful monitoring and response to adverse reactions. In addition, we need to optimize the stability, small molecule toxicity, clearance rate and other PK/PD parameters from the ADC molecule itself in order to find a new generation of safer ADCs.

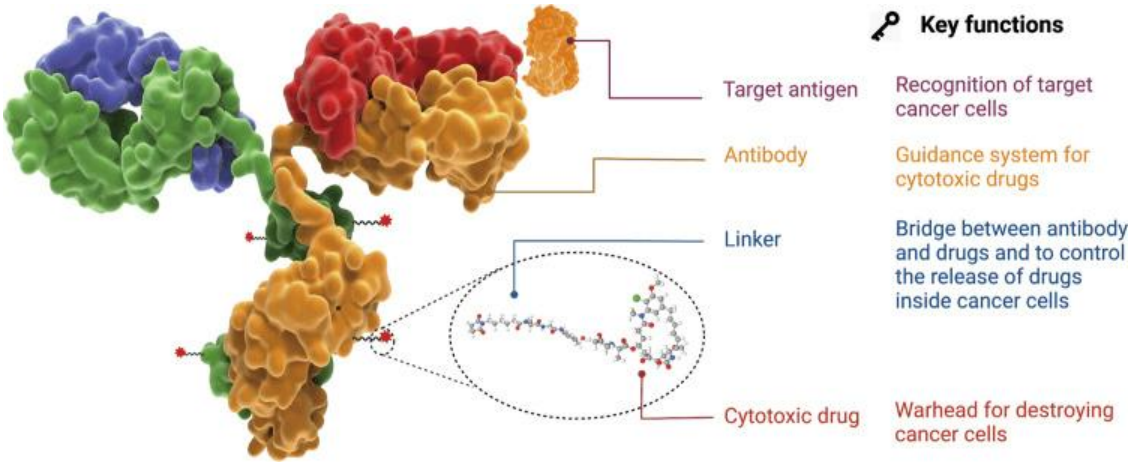

Figure 1. Antibody-drug conjugates

Approved ADCs Worldwide

Antibody-drug conjugates consist of antibodies, linkers and toxic small molecules, which combine the high specificity of antibodies with the potent killing ability of toxin molecules to precisely target and kill tumor cells. ADCs have become an important component of clinical oncology therapy and are currently a hot spot for innovative drug development.

As of December 2022, there are 15 ADC drugs approved globally, including 12 approved by the FDA, with indications including solid tumors and hematologic tumors.

Drugs (Company)	Trade Names	Target antigens	Approved Countries	Approved Date	Approved Indications
Hematological malignancies					
Gemtuzumab ozogamicin (Pfizer)	Mylotarg®	CD33	FDA/EMA/PMDA	2000/5/17; 2017/9/1	newly-diagnosed CD33-positive AML to include pediatric patients 1 month and older.
Brentuximab vedotin (Seagen)	Adcetris®	CD30	FDA/EMA/PMDA/NMPA	2011/8/19	R/R CD30 positive HL and systemic ALCL; in combination with chemotherapy including the treatment of certain types of PTCL and previously untreated stage III or IV cHL.
Inotuzumab ozogamicin (Pfizer)	Besponsa®	CD22	FDA/EMA/PMDA/NMPA	2017/6/28	adults with R/R B-cell precursor ALL.
Moxetumomab pasudotox (AstraZeneca)	Lumoxiti®	CD22	FDA/EMA	2018/9/13	adult patients with R/R HCL who have previously failed to receive at least two systemic therapies (including purine nucleoside analogs).
Polatuzumab vedotin (Roche)	Polivy®	CD79B	FDA/EMA	2019/6/10	in combination with bendamustine plus rituximab for the treatment of patients with R/R DLBCL, who have received at least two prior therapies.
Belantamab mafodotin (GSK)	Blenrep®	BCMA	EMA	2020/8/5	adult patients with R/R MM who have received at least four treatments, including anti-CD38 monoclonal antibodies, proteasome inhibitors and immunomodulators
Loncastuximab tesirine (ADC Therapeutics)	Zynlonta®	CD19	FDA	2021/4/23	adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low grade lymphoma and high-grade B-cell lymphoma
Solid Tumors					
Ado-trastuzumab emtansine (Roche)	Kadcyla®	HER2	FDA/EMA/PMDA/NMPA	2013/2/22	adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.
Enfortumab vedotin (Seagen)	Padcev®	Nectin-4	FDA	2019/12/18	locally advanced or metastatic urothelial cancer who have previously received platinum chemotherapy and a PD-L1/PD-1 inhibitor
Fam-trastuzumab deruxtecan (Daiichi Sankyo)	Enhertu®	HER2	FDA/EMA/PMDA	2019/12/20	adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting; locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen
Sacituzumab govitecan (Immunomedics)	Trodelvy®	Trop-2	FDA/NMPA	2020/4/22	patients with unresectable locally advanced or metastatic TNBC who have received two or more prior systemic therapies
Cetuximab sarotalocan (Rakuten Medical)	Akalux®	EGFR	PMDA	2020/9/25	unresectable locally advanced or recurrent HNSCC
Disitamab vedotin (RemeGen)	Aidixi®	HER2	NMPA	2021/6/8	patients with locally advanced or metastatic gastric cancer (including gastroesophageal junction adenocarcinoma) who have received at least 2 types of systemic chemotherapy
Tisotumab vedotin (Genmab/Seagen)	Tivdak®	TF	FDA	2021/9/20	adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy
Mirvetuximab soravtansine (ImmunoGen)	ELAHERE™	FRα	FDA	2022/11/14	epithelial ovarian, fallopian tube, or primary peritoneal cancer

Figure 2. Approved ADCs

Toxic Side Effects of ADCs

The "magic bullet" ADC could provide significant clinical benefits to patients and even change the way oncology is treated.

Adcetris, developed by Seagen to target CD30, has become a first-line therapy for refractory Hodgkin's lymphoma and peripheral T-cell lymphoma, improving patient outcomes.

Daiichi Sankyo/AstraZeneca's DS-8201, on the other hand, has revolutionized the entire HER2+ breast cancer treatment landscape, with equally excellent efficacy in patients with HER2- breast cancer. In the DESTINY-Breast04 trial presented at ASCO this year, **DS-8201 extended median progression-free survival from 5.4 months to 10.1 months and median overall survival from 17.5 months to 23.9 months for patients with HER2 low-expressing breast cancer compared to chemotherapy**, achieving a breakthrough in the efficacy of HER2-targeted agents in patients with HER2 low-expressing breast cancer. On August 5, 2022, the FDA approved DS-8201 for unresectable or metastatic HER2 low-expressing breast cancer, rewriting the classification criteria for breast cancer.

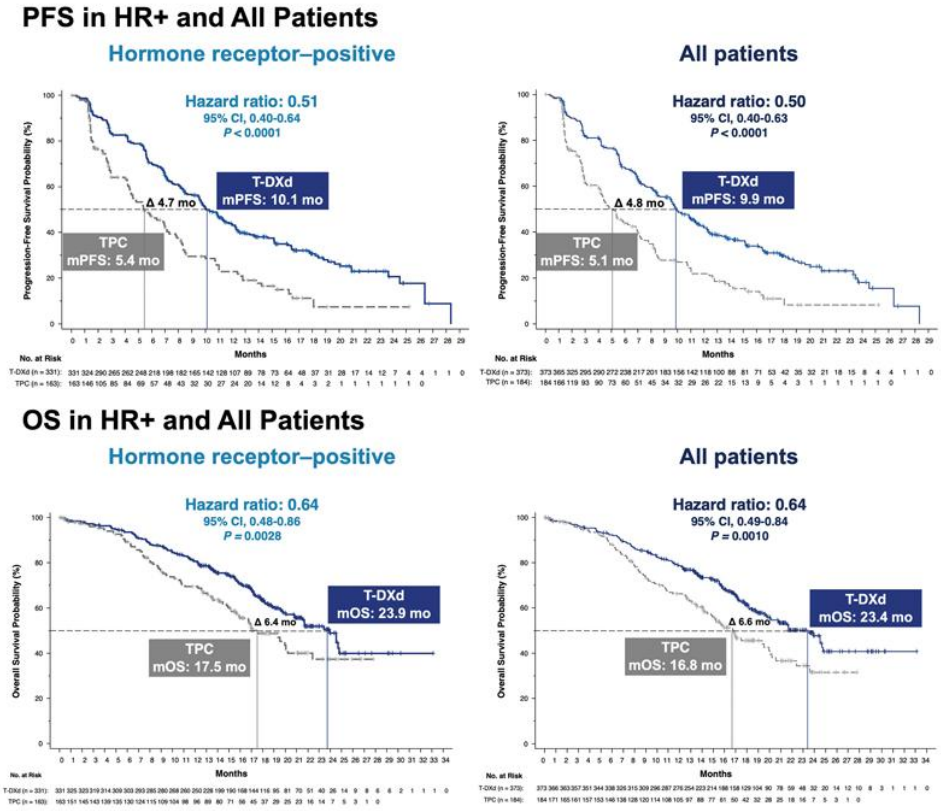

Figure 3. Progression-Free Survival and Overall Survival Results in HR-Positive and All Patient Populations from the DESTINY-Breast04 Trial

On August 11, 2022, the FDA also accelerated the approval of DS-8201 for non-small cell lung cancer with HER2 mutations, making it the first HER2-targeted therapy for lung cancer.

However, the multiple combinations of antibody-linker-toxin molecules are like a double-edged sword, which brings powerful efficacy to ADC drugs, but also brings the disadvantage of higher incidence and severity of toxic side effects than general monoclonal antibodies and small molecules.

Among the 12 ADCs approved by the FDA, only Loncastuximab tesirine targeting CD19 approved in 2021 and Polatuzumab vedotin targeting CD79 approved in 2019 were not added with black box warnings, while the remaining 10 ADCs were added with black box warnings. The probability of black box warnings is much higher than that of common small molecules and monoclonal antibodies, and the toxicities involved include severe hepatotoxicity, ocular toxicity, severe skin reactions, neutropenia, progressive multifocal leukoencephalopathy and interstitial lung disease (ILD).

(1) According to a meta-analysis encompassing 169 clinical trials with a total of 22,492 patients [1], the overall incidence of all grades of adverse reactions when treated with ADC drugs was 91.2%, and the incidence of grade ≥ 3 adverse reactions was 46.1%, with common adverse reactions similar to those reported with chemotherapy drugs, such as lymphocytopenia (53.0%), nausea (44.1%), neutropenia (43.7%), blurred vision (40.5%), and peripheral neuropathy (39.6%), which were mainly dose-limiting off-target toxicities. Patient death due to ADC treatment was reported in 153 of these 169 studies, with an overall incidence of 1.3%, and the immediate causes of death were primarily pneumonia, sepsis, and respiratory failure.

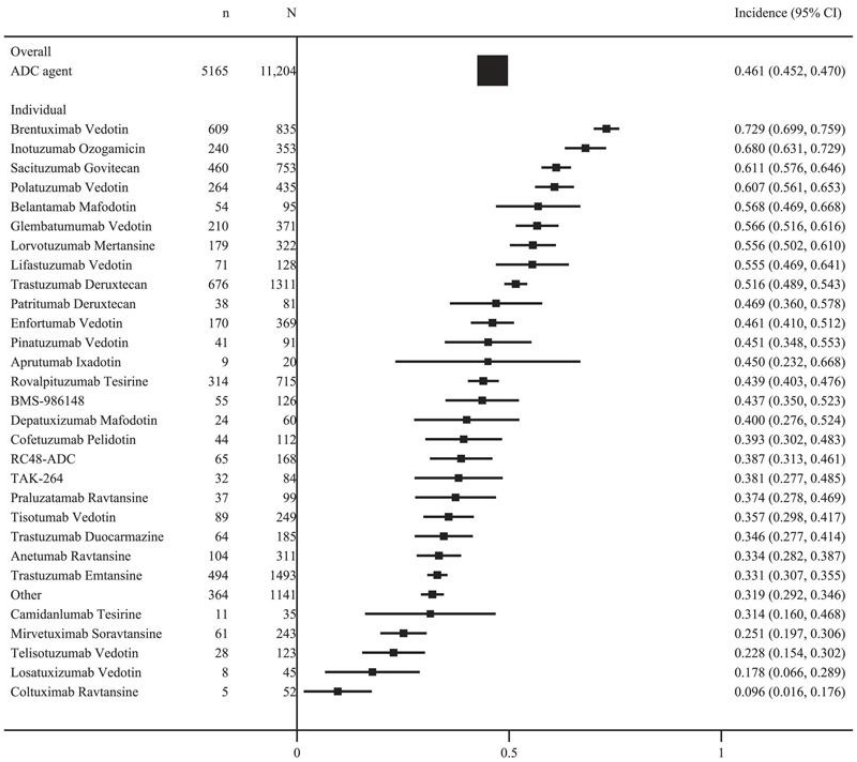

Figure 4. The overall incidence of grade ≥3 treatment-related adverse events in ADC regimens. ADC indicates antibody–drug conjugate. Source: rference [1]

(2) The spectrum and incidence of adverse reactions vary for different ADC drugs. the results of the DESTINY-Breast 01 trial showed that the adverse reactions of Enhertu were mainly deruxtecan-related side effects, such as nausea (79%), decreased white blood cell count (70%), decreased hemoglobin (70%), decreased neutrophil count (62%), fatigue (59%), vomiting (47%), alopecia (46%), increased aspartate aminotransferase (41%), increased alanine aminotransferase (38%), decreased platelet count (37%), constipation (35%), decreased appetite (32%), anemia (31%), diarrhea (29%), hypokalemia (26%), and cough (20%), with a 9% incidence of interstitial lung disease warned by black boxes and a 2.6% incidence of death due to interstitial lung disease [5].

(3) The recently approved Mirvetuximab Soravtansine, on the other hand, has a black box warning added for ocular toxicity, which may cause serious ocular side effects including visual disturbances, keratopathy, dry eye, and uveitis. According to safety data presented at the 2022 ASCO Congress [7], the most common adverse effects of Mirvetuximab Soravtansine included blurred vision (63%), fatigue (58%), keratopathy (43%), and dry eye (35%). This is similar to Belantamab mafodotin developed by GSK, whose main adverse effect was also ocular toxicity, probably due to the tendency of the payload of both to accumulate in the corneal epithelium.

Off-Target Toxicity as a Major Source of Adverse Reactions

Both cytotoxic drugs and antibodies of ADC can affect normal cells, which can lead to adverse reactions. **Its adverse reactions can be divided into on-target and off-target toxicity,** where on-target toxicity refers to the killing of normal tissues expressing target antigens by ADC drugs and off-target toxicity refers to the killing of ADCs in tissues not expressing target antigens. According to clinical observations, off-target toxicity caused by cytotoxic drugs is the main source of ADC adverse reactions.

On-target toxicity: Antibody-mediated ADCC and CDC effects can all occur on normal cells expressing the target antigen and lead to adverse effects, such as secondary renal injury. In addition, antibodies can also block the signaling of normal cellular target antigens, for example, HER2-targeted ADC can act on HER2-expressing lung epithelial cells, cardiomyocytes, and cause adverse effects such as lung injury, hepatotoxicity, and reduced LVEF by either blocking the HER2 pathway by antibodies or direct killing by cytotoxic drugs.

Off-target toxicity: The shedding of cytotoxic drugs in the circulation, the bystander killing effect on normal cells, and the endocytosis/uptake of ADCs by normal cells can lead to off-target toxicity, exposing normal cells to damage by cytotoxic drugs. Lymphocytes, granulocytes, and platelets in the circulation are the first to suffer damage, followed by the liver, which tends to accumulate lipophilic small molecules, and the kidneys, where the drug is excreted, as well as the lungs, nerves, skin, and other tissues, causing adverse reactions similar to those observed clinically with chemotherapy drugs.

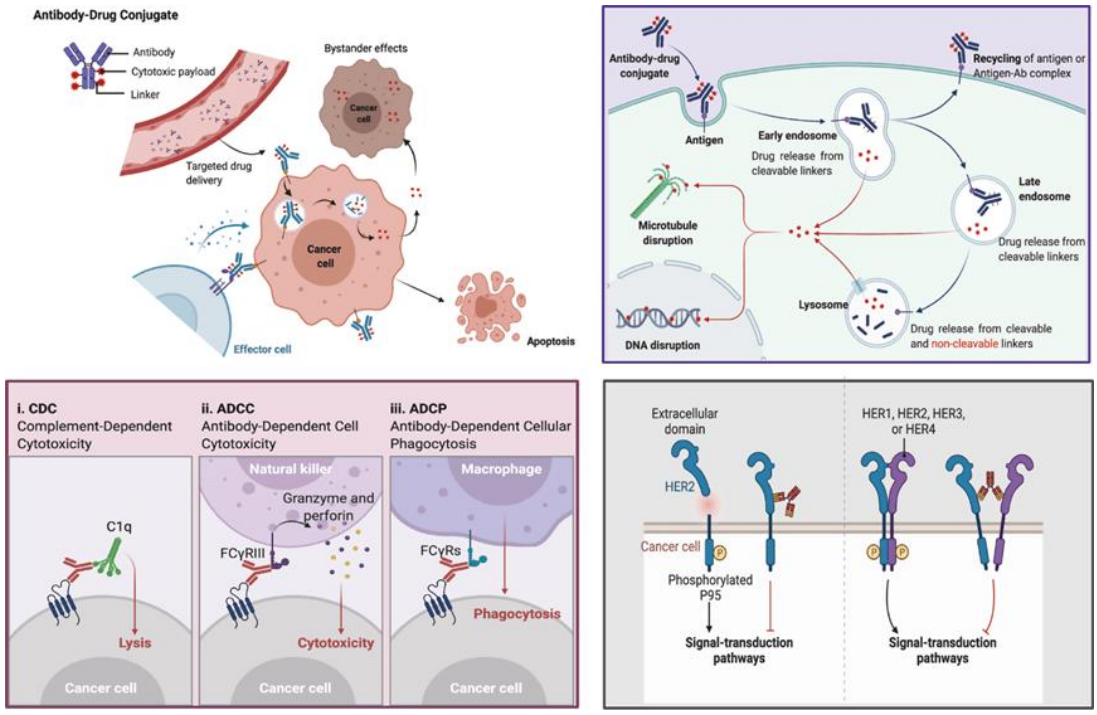

Figure 5. The overview of the mechanisms of ADC for killing cancer cells via different approaches. (Fu, 2022)

Conclusion

ADC drugs have benefited many oncology patients by improving the targeting of small molecules by linking cytotoxic drugs to antibodies. However, current ADC drugs have not yet demonstrated better safety than chemotherapeutic small molecules or monoclonal antibodies due to significantly higher payload toxicity and unstable linker circulation.

Therefore, on the one hand, we need to monitor and manage the risk of side effects in the clinical application of ADCs and respond to the adverse effects in a timely manner; on the other hand, we need to continuously optimize their antibodies, linkers and cytotoxic drugs to improve PK/PD properties and enhance delivery efficiency, so as to achieve strong drug efficacy under weak toxicity.

References:

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