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Review Article

Comprehensive Overview on Antibody Drug Conjugates- A Promising Approach in Cancer Therapy

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Abstract

Chemotherapy remains a cornerstone in cancer treatment, utilizing cytotoxic agents to kill or inhibit the growth of cancer cells. However, its efficacy is often limited by systemic toxicity and the development of resistance. To address these challenges, Antibody-Drug Conjugates (ADCs) have emerged as a promising therapeutic strategy, combining the specificity of monoclonal antibodies with the potency of cytotoxic drugs. ADCs are designed to deliver targeted chemotherapy directly to cancer cells, reducing off-target effects and improving therapeutic outcomes. The structure of ADCs consists of a monoclonal antibody, a cytotoxic agent (payload), and a chemical linker. The antibody specifically binds to tumor-associated antigens, facilitating internalization of the drug, which is then released within the cancer cell to induce cell death. This selective targeting minimizes the damage to normal, healthy tissues. Since the first ADC approval in 2000, the field has rapidly advanced, with multiple ADCs receiving FDA approval for both hematological and solid tumors. Despite their potential, ADC development faces challenges such as linker stability, payload delivery, and tumor penetration. Recent advancements have led to the development of second and third-generation ADCs, which feature improved stability, efficacy, and safety profiles. The future of ADCs lies in optimizing their design, including selecting appropriate antigens, refining drug-to-antibody ratios, and enhancing intracellular delivery mechanisms. Overall, ADCs represent a transformative approach to cancer therapy, offering a more targeted, effective, and safer treatment option for cancer patients.

Keywords: ADC, Cancer, Chemotherapy, Cytotoxic drug, Carrier, Linker, Target therapy, Toxicity.

INTRODUCTION

Cancer is a group of diseases characterized by uncontrolled cell growth and spread, often forming tumors that can be benign or malignant. Malignant tumors can invade surrounding tissues and metastasize to other body parts. Cancers arise from various tissues and are classified by their cell type, with common types including breast, lung, prostate, and colorectal cancers[1]. Causes of cancer include genetic factors, environmental exposures like tobacco smoke and radiation, and lifestyle choices such as diet and exercise. It is a leading cause of death globally, responsible for nearly 10 million deaths in 2020. Each year, around 400,000 children develop cancer, with the most common types varying by country. Cervical cancer is most common in 23 countries [2].

Chemotherapy is a primary cancer treatment, using cytotoxic drugs to kill cancer cells or alleviate symptoms. These drugs include Alkylating agents, platinum drugs, Antimetabolites, Microtubule-damaging agents, and Topoisomerase inhibitors. Alkylating agents and platinum drugs bind to cellular macromolecules like DNA, interfering with cell division and gene expression. Antimetabolites disrupt DNA and RNA synthesis by mimicking normal molecules. Topoisomerase inhibitors block enzymes crucial for DNA repair, replication, and transcription. Microtubule agents disrupt the cytoskeleton, halting cell growth[3]. Despite their use, chemotherapy often lacks significant antitumor effects.

Other conventional cancer treatments include targeted therapy, immunotherapy, surgery, radiation, stem cell therapy, laser therapy, and photodynamic therapy. However, chemotherapy and other therapies have limitations due to their narrow therapeutic index and non-selective action, causing systemic toxicity. While targeted therapy and immunotherapy have improved survival and mortality rates, resistance to these treatments often develops, necessitating alternative approaches [4].

To improve the therapeutic index of an anticancer drug the minimum effective dose (MED) should be reduced or the maximum tolerated dose (MTD) should be

elevated. This can be achieved either by improving the potency of the cytotoxic agent to reduce the MED or by elevating the tumor selectivity thereby increasing the MED. Moreover, a combination of these two properties in a therapeutic agent would be a remarkable solution to improve the therapeutic index of an anti-cancer agent[5].This gave rise to the potential clinical strategy of using highly cytotoxic agents and specific cell targeting molecules together in the form of antibody drug conjugates (ADC's). In ADC's, a monoclonal antibody is conjugated with a cytotoxic agent using a chemical linker[6]. ADC's harnesses the power of both cytotoxic chemotherapy and targeted therapy showing promising efficacy with limited toxicities compared to conventional treatment. The ultimate goal of an ADC is to maximize tumor cell kill, while minimizing systemic toxicity to healthy cells.

IMPORTANCE OF ADC'S IN CANCER

Once ADCs are administered intravenously, it enters the blood stream and the antibody components that are specifically designed to track a particular tumor antigen, recognizes and bind to the surface of the cancer cell. This ADC is later internalized by the cancer cell through endocytosis and processed within endosomes or lysosomes resulting in cleavage of linker holding the Antibody and cytotoxic payload[7]. For ADCs with cleavable linkers, the cleavage mechanisms (e.g., hydrolysis, proteolytic cleavage or reductive cleavage) occur in endosomes and ADCs with non-cleavable linkers require complex proteolytic cleavage in lysosomes by cathepsin B and plasmin. The release of payload causes damage to the DNA strands or inhibits the polymerization of topoisomerase or RNA leading to cell death. ADCs are safe for non-cancerous cells because the ADCs in interaction with the human neonatal Fc receptor (FcRn) form a complex and ADC-bound FcRn is recycled and sent back to the cell surface. This mechanism of recycling prevents any harm to the noncancerous cells in case of misdelivery[8].

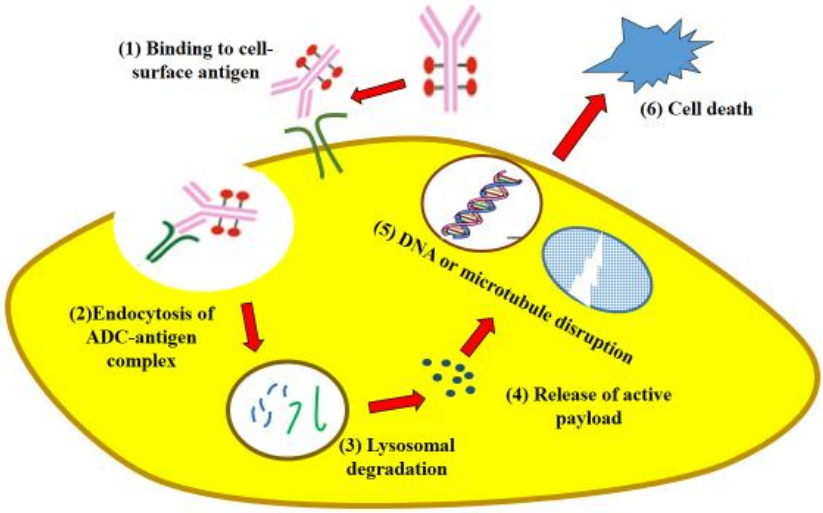

Figure 1: Mechanism of action of ADC. The ADC binds to its target cell-surface antigen receptor (Step1) to form an ADC-antigen complex, leading to endocytosis of the complex (Step 2). The internalized complex undergoes lysosomal processing (Step 3) and the cytotoxic payload is released inside the cell (Step 4). The released payload binds to its target (Step 5), leading to cell death (Step 6)[8].

TIMES OF ADC

Historical Background of ADC Development:

The concept of targeted chemotherapy was first proposed by German scientist Paul Ehrlich in the early 20th century. He envisioned a "magic bullet" that could selectively deliver toxins to diseased cells while sparing healthy tissues. This idea laid the foundation for the later development of ADCs, which utilize cell surface antigens to guide the delivery of cytotoxic agents[9]. The hybridoma technology developed in the 1970s to produce monoclonal antibodies (mAbs) enabled the realization of Ehrlich's vision, leading to the first human ADC trials in the 1980s. The initial breakthrough came with the approval of Gemtuzumab Ozogamicin in 2000, a CD33-targeting antibody conjugated to the cytotoxic drug calicheamicin.[9]

Development and Approvals:

Since the early 2000s, ADCs have evolved significantly. In 2009, Gemtuzumab Ozogamicin was the only FDA-approved ADC, with several others in clinical trials. Today, more than 10 ADCs have received FDA approval, with many others undergoing clinical evaluation.[2] The approval of Kadcyla in 2013 marked the first ADC approved for solid tumors, followed by other notable ADCs like Padcev, Enhertu, and *Trodelvy. These approvals have demonstrated ADCs' potential not only in haematological cancers but also in solid tumors, where the treatment landscape has seen significant advancements.[9]

Challenges and Progress:

Despite the promising potential of ADCs, their development has been fraught with challenges. Early ADCs faced issues such as unstable linkers, premature

release of cytotoxic agents, and inadequate delivery of the payload to tumor cells. The first FDA-approved ADC, Mylotarg (gemtuzumab ozogamicin), encountered these problems, leading to its market withdrawal in 2010. However, after modifying the dosing regimen, it was re-approved in 2017 for acute myeloid leukemia (AML).[10]

The 2010s saw the development of second-generation ADCs, which addressed some of the issues with linker stability and payload delivery. For example, Adcetris (brentuximab vedotin) and Kadcyla (trastuzumab emtansine) demonstrated improved targeting and lower toxicity profiles, though still carrying important safety warnings.[10]

Third-Generation ADCs: Advances in Linker and Payload Technology:

The period from 2017 to 2020 witnessed the approval of third-generation ADCs, which benefited from advances in linker technology and payload optimization. The new generation of ADCs, such as Polivy (polatuzumab vedotin), Padcev (enfortumab vedotin), and Enhertu (trastuzumab deruxtecan), showcased enhanced stability, better tumor penetration, and the ability to carry larger cytotoxic payloads. These innovations have improved the efficacy and safety of ADCs, prompting a resurgence in their clinical application.[11]

DESIGN AND STRUCTURE OF ADC

Factors affecting ADC design and activity[12]

- The selection of the target antigen to which the ADC binds is, perhaps, the most critical factor in developing an effective molecule.
- The number of target molecules expressed on the tumor cell surface, their differential expression on tumor versus normal cells
- The rate of internalization and route of intracellular trafficking
- Whether the target is amenable to selecting an antibody with intrinsic biologic activity.

Monoclonal antibody: The monoclonal antibody is an important component of the ADC structure. It is targeted against a specific antigen with minimal immunogenicity and cross-reactivity. Among several immunoglobulins the IgG type is preferred because it is easy to produce, it has a reduced clearance from the systemic circulation and it can provide highly efficient complement-dependent cytotoxicity (CDC) and antibody-dependent cytotoxicity (ADCC).

Cytotoxic drug: It is also called as the "payload" or "warhead". The microtubule damaging agents and DNA-damaging agents are the two most commonly used cytotoxic agents in ADC's. The ideal properties of a cytotoxic agent include remarkable stability in circulation, low molecular weight, prolonged half-life and low immunogenicity. The drug-to-antibody ratio (DAR) is an important factor to be considered during the development of an ADC. Very high DAR can cause off-target toxicity and elevate plasma concentration whereas low DAR may not provide the desired therapeutic outcome. The optimal DAR for most ADCs, however, ranges from 2 to 8 drugs/antibody.

Linker: A linker functions as a link between the monoclonal antibody with cytotoxic agents. An ideal linker should be stable in the circulation and should be cleaved within the cancer cell and release the cytotoxic agent. Based on the mechanism of action linkers can be classified as cleavable and non-cleavable linkers. No cleavable linker like thioesters are more stable than cleavable linkers and they release the payload by lysosomal degradation whereas the cleavable linkers release their payload depending on the endosome's physiological condition.[13]

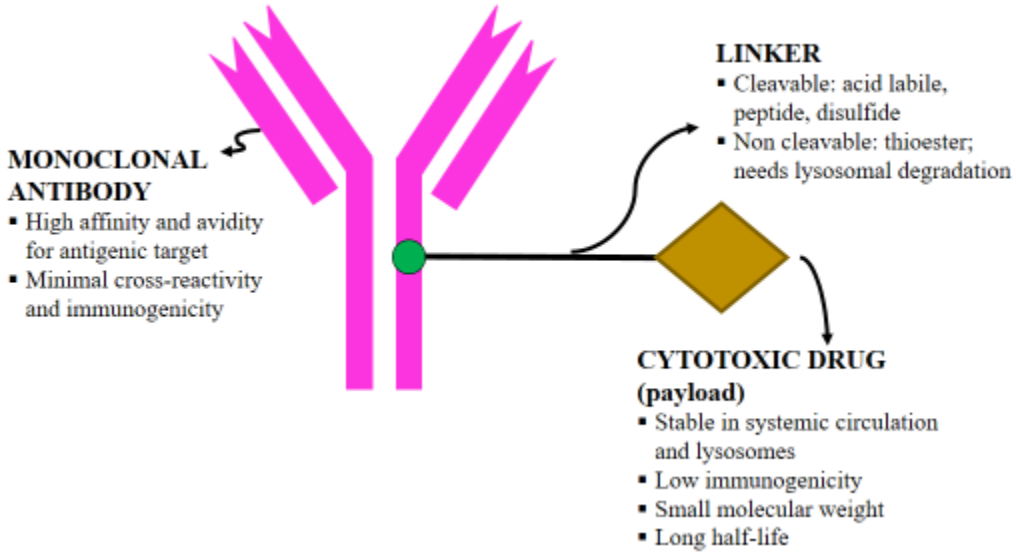

Figure 2: Diagram of an antibody-drug conjugate. While the antibody (the pink Y-shape) provides selectivity and drives the drug to the right place, the drug (in yellow) does the work in the same way traditional chemotherapies do. The linker (in black) has to be strong enough not to be cleaved while travelling through the body, but still easily cleavable by enzymes once it has reached the interior of cancer cells (for internalizing ADCs) or their surroundings (for non-internalizing ADCs).[13]

CONJUGATION METHOD

One of the most important steps in ADC development is the conjugation of the antibody to the cytotoxic payload via a chemical linker. The conjugation method directly influences the homogeneity and stability of the ADC.

- **Amide Coupling**: The most widely used conjugation method involves the formation of an amide bond between the cytotoxic drug and a lysine residue on the antibody. This reaction typically utilizes the carboxyl group of the drug and the amine group of lysine. Amide coupling is used in well-known ADCs such as **Gemtuzumab Ozogamicin** and **T-DM1**[14]. This method is straightforward but can lead to heterogeneous ADC populations, as antibodies contain multiple lysine residues that may react with the drug.
- **Cysteine-Based Conjugation**: Alternatively, disulfide bonds within the antibody can be reduced to expose cysteine thiol groups, which can then be conjugated to the payload. This approach can result in a more controlled conjugation site, especially when site-specific conjugation is used.[15]Cysteine-based conjugation is often employed in **homogeneous ADCs**, where greater precision is required for optimal therapeutic outcomes.

Lysine and Cysteine Residue as Conjugation Sites

The natural amino acid residues available for conjugation in antibodies—lysine and cysteine—are critical considerations for the design of ADCs.

- **Lysine Residues**: Antibodies typically contain 80-100 lysine residues, most of which are surface-exposed and available for conjugation[16]. However, due to the large number of lysine residues and their diverse locations on the antibody surface, the conjugation process can lead to heterogeneous ADCs. This variability can result in differences in drug-to-antibody ratios (DARs), which affect the pharmacokinetics (PK), biodistribution, and therapeutic efficacy of the ADC[17].
- **Cysteine Residues**: Cysteine residues, which are involved in the formation of disulfide bonds, can be targeted after the reduction of the antibody's disulfide linkages. Reduced cysteine residues are often used in **site-specific conjugation** strategies to produce more homogeneous ADCs[18]. Such ADCs typically exhibit improved stability and more predictable PK profiles compared to their heterogeneous counterparts.

Heterogenous vs Homogeneous ADCs

- **Heterogeneous ADCs**: In the case of heterogeneous ADCs, the conjugation occurs at multiple lysine or cysteine sites, leading to a mixture of conjugates with varying drug-to-antibody ratios (DARs). This heterogeneity can create pharmacokinetic challenges, such as variability in drug distribution, clearance rates, and off-target effects.[19]
- **Homogeneous ADCs**: Homogeneous ADCs, on the other hand, are engineered to ensure that a specific number of payload molecules are conjugated to precise sites on the antibody. This is typically achieved through the use of site-specific conjugation techniques, such as the introduction of engineered cysteine or lysine residues.[20] These ADCs tend to have better pharmacokinetics, more consistent therapeutic efficacy, and a more predictable safety profile compared to heterogeneous ADCs.[21]

Linkers Chemistry in ADC Design

The linker between the antibody and the payload is another essential factor influencing ADC performance. The linker must be chemically stable in the bloodstream to avoid premature release of the cytotoxic agent but also cleavable inside the target cell, often via enzymatic or pH-sensitive mechanisms.

- **Cleavable Linkers**: These linkers are designed to be broken inside the target cell, usually in response to enzymatic activity or acidic pH in the lysosome. This enables the controlled release of the cytotoxic payload at the site of action.[22]
- **Non-Cleavable Linkers**: Non-cleavable linkers are more stable and ensure that the payload remains attached to the antibody until the entire conjugate is internalized and degraded within the cell. However, the payload is not released until the entire ADC is degraded, which may impact its efficacy in certain cases.

POTENTIAL CHALLENGES IN THE DEVELOPMENT AND THE APPLICATION

First-generation ADCs faced multitudinous challenges, similar to poor systemic linker stability, low excrescence internalization, low lading capacity, off-target toxin, short circulating occupant times and immunogenicity and medicine resistance. A critical aspect of developing antibody-medicine conjugates (ADCs) is icing their particularity to target cells, which is essential for minimizing out-target toxins caused by their potent cytotoxic agents. Assessing particularity frequently involves using ways similar to inflow cytometry and immunohistochemistry (IHC). Flow cytometry helps in assaying the expression of target antigens on the cell face, furnishing quantitative data on how well the ADC binds to its willed target cells. Immunohistochemistry complements this by allowing for the localization and visualization of the ADC within towel samples, thereby attesting to its list particularity. IHC can reveal whether the ADC is simply binding to the target cells and not affecting non-target cells. By combining both ways, experimenters can more directly assess the safety and efficacy of ADCs. This binary approach helps in relating and mollifying the pitfalls associated with out-target goods, which are pivotal for icing patient safety and perfecting remedial issues. These combined methodologies enhance the perfection of ADCs, making them more effective in targeting cancer cells while reducing the liability of adverse side goods. Eventually, this thorough evaluation process is vital for the successful development of ADCs in cancer

remedies.[23] Current ADC programs are fastening on specific monoclonal antibodies (mAbs) that more attach to linkers and opting for optimal cytotoxic medicines. A primary exploration thing is modifying the spots on the mAb where the linker attaches. Preliminarily, ADCs had multiple linkers attached to each antibody, creating miscellaneous liaisons. This made it difficult to optimize the medicine-to-antibody rate (DAR) and ensure batch unity. By generating homogeneous ADCs where each antibody has the same number of linker groups, particularity improves. This can be achieved using point-specific conjugation to direct linker attachment to specific antibody locales. Catalent developed the SMARTag ® point-specific bioconjugation technology, which encodes a string of six amino acids into the antibody. A particular enzyme recognizes this sequence and converts a cysteine residue within it into a formyl glycine residue. The formyl glycine contains an aldehyde functional group that acts as a handle for point-specific conjugation, performing in the conformation of a largely stable C- C bond connecting the antibody to the linker group.

TRPH- 222 is a CD22- directed antibody- medicine conjugate (ADC) developed using Catalent's SMARTag ® point-specific bioconjugation technology, which allows for precise attachment of the cytotoxic medicine to specific spots on the antibody, performing in a homogeneous ADC with harmonious medicine- to antibody rates. Targeting CD22, a cell face protein expressed on B-cells, shows implicit for treating B-cell malice similar to non-Hodgkin's carcinoma. Presently in Phase I clinical trials for regressed/ refractory non-Hodgkin's carcinoma, TRPH-222 has demonstrated the capability to be administered at boluses up to 10 milligrams per kilogram, significantly advanced than typical ADC boluses, indicating advanced safety and efficacy. By binding to CD22 on B- -cells and delivering its cytotoxic cargo directly into cancer cells, TRPH-222 aims to minimize off-target goods and enhance remedial issues.[24]

TESTING: testing of free medicine poison situations in an ADC medication during release and stability to ensure the free medicine poison remains insave situations. Polymeric lab ware which is used for the storehouse of biologics can strain composites that have hydrophobicity and those with UV immersion biographies analogous to the free medicine. Thus, it is important to ensure that extractable and leachable won't intrude with free medicine analysis.

MANUFACTURING: The manufacture of ADCs retains multiple hurdles which include relating suitable target antigens, enhancing antibodies, linkers, and loads, and managing resistance mechanisms and side goods. Some of the unique challenges are

Analytical Method Transfers Compliance with cGMP specifications demands precise medicine-to-antibody rate (DAR) and cell-grounded energy assays. Variability in styles and outfits between guests and CMOs can complicate the process. Effective collaboration and in-person training can ensure successful system transfers.

Conjugation Technology Transfers combining biologics with largely potent small motes necessitates technical constraint outfit and moxie. Variations in conjugation chemistries and raw accoutrements bear strict process control and verification for thickness. The presence of person-in-factory (PIP) during original manufacturing is frequently profitable.

Scale-spanning ADC manufacturing introduces process variations due to different outfits, raw accoutrements, and response conditions. Using gauged-down models that mimic clinical-scale manufacturing helps address these challenges.

Communication Transparent and effective communication between guests and CMOs is essential. Assessing CMOs for their experience, outfit, and cooperative capabilities ensures smoother design prosecution.

CMO Installation Capabilities CMOs need advanced installations with anchorite, lyophilization capabilities, and applicable engineering controls for ADC products. Using single-source CMOs can streamline force chains, reduce pitfalls, and accelerate time-to-request by integrating all stages of ADC manufacturing.

Efforts are presently underway to sequence colorful ADCs with new loads and interpret on preliminarily unknown variables in ADC sequencing. This is particularly material for HR-positive bone cancer (BC) treatment. Especially, T-DXd and Sacituzumab Govitecan have shown remarkable response rates in cases with advanced, pretreated HR-positive BC and are presently in phase 3 trials. However, two distinct ADCs with topoisomerase- I impediments could be introduced for cases with pretreated HR-positive BC If these trials yield positive results.

An encouraging illustration is handed by the original anti-HER2 ADC, T- DM1, which is largely efficient and approved for treating HER2-positive BC cases who have progressed on taxanes. Given that taxanes, like DM1, function through microtubule dislocation, employing an analogous chemotherapeutic agent via an indispensable strategy might sustain antitumor exertion, indeed within the environment of ADC sequencing.[25]

The main challenge in medicine manufacturing is ensuring a constantly effective product that's pure, safe from impurity, and cost-effective, while also guarding workers and the terrain. For ADCs, this begins with high-quality monoclonal antibodies (mAbs). The adding focus on ADCs is egging manufacturers to prioritize the manufacturability of mAbs by optimizing their physical and chemical parcels to repel the demanding product processes. unborn ADCs are anticipated to incorporate new natural factors, similar to lower antibody-deduced list units and biospecific target-binding motes, taking adaptations to traditional mAb processing styles and new sanctification ways. These advancements will drive further invention in mAb expression and processing.

Developing ADCs is complex due to the need to optimize additional steps not present in conventional monoclonal antibody (mAb) manufacturing, such as antibody-drug

conjugation and subsequent purification. The drug-antibody ratio (DAR) is critical for determining the ADC's potency and therapeutic index. Excessive modification of the mAb can negatively affect its biological and pharmacological properties, impacting tolerance, targeting efficiency, and stability. Optimizing conjugation chemistry and linkers is essential. Approved ADCs often use broad specificity chemistries targeting natural amino acid side chains, but controlling drug incorporation is crucial for efficacy and regulatory compliance.

Additional considerations include managing mAb aggregates and side reactions during conjugation, which pose purification and analytical challenges. Understanding critical reaction parameters and their interactions is vital, often assessed through statistical design of experiments. High-throughput screening methods, while requiring additional investment, enhance efficiency. Monitoring DAR can be done using techniques like RP-HPLC, HIC, or analytical IEX, and size exclusion chromatography detects oligomers and aggregates. Innovations in site-specific conjugation chemistries are improving precision, targeting unique mAb sites, sometimes incorporating non-natural amino acids into the protein structure for enhanced stability and specificity.[26]

CURRENTLY APPROVED ADC'S BY US[27,28,29]

TRADE NAME	APPROVAL YEAR	DRUG	PAYLOAD	COMPANY	INDICATION
Mylotarg	2017	Gemtuzumab ozogamicin	Gemtuzumab ozogamicin	Pfizer/Wyeth	Acute myelogenous leukemia (AML)
Adcetris	2011	Brentuximab vedotin	Brentuximab vedotin	Seagen/Takeda	Hodgkin lymphoma, anaplastic large cell lymphoma
Kadcyla	2013	Trastuzumab emtansine	Trastuzumab emtansine	Genentech/Roche	HER2-positive metastatic breast cancer
Besponsa	2017	Inotuzumab ozogamicin	Inotuzumab ozogamicin	Pfizer/Wyeth	B-cell precursor acute lymphoblastic leukemia (ALL)
Lumoxiti	2018	Moxetumomab pasudotox	Moxetumomab pasudotox	AstraZeneca	Hairy cell leukemia (HCL)
Polivy	2019	Polatuzumab vedotin-piiq	Polatuzumab vedotin-piiq	Genentech/Roche	Diffuse large B-cell lymphoma (DLBCL)
Padcev	2019	Enfortumab vedotin	Enfortumab vedotin	Astellas/Seagen	Advanced urothelial cancer
Enhertu	2019	Trastuzumab deruxtecan	Trastuzumab deruxtecan	AstraZeneca/Daiichi Sankyo	HER2-positive breast cancer
Trodelvy	2020	Sacituzumab govitecan	Sacituzumab govitecan	Gilead Sciences	Triple-negative breast cancer (TNBC)
Blenrep	2020 (Withdrawn 2022)	Belantamab mafodotin-blmf	Belantamab mafodotin-blmf	GlaxoSmithKline (GSK)	Multiple myeloma (withdrawn due to efficacy issues)
Zynlonta	2021	Loncastuximab tesirine-lpvl	Loncastuximab tesirine-lpvl	ADC Therapeutics	Large B-cell lymphoma
Tivdak	2021	Tisotumab vedotin-tftv	Tisotumab vedotin-tftv	Seagen/Genmab	Metastatic cervical cancer
Elahere	2022	Mirvetuximab soravtansine	Mirvetuximab soravtansine	ImmunoGen	Platinum-resistant ovarian cancer

MECHANISMS OF RESISTANCE TO ADCS

Drug resistance consists of the failure or reduction of the effectiveness of a treatment. Such failure/ reduction may have evolved after treatment with the drug (secondary or acquired resistance) or may be present from the start of the treatment (primary or de novo resistance).In principle, mechanisms of resistance to ADC should be similar to those raised against the individual components of the ADC, namely the mAb and the cytotoxic drug[30]

Antigen-related resistance

ADCs are targeted therapeutics, and the soon-predicted mechanism of resistance could consist of changes in the levels of the antigen recognized by the mAb.

Defects in internalization and trafficking pathways

ADC optimal efficacy requires endocytic uptake of the antibody into the cell. Endocytosis can occur by different internalization routes such as clathrin-mediated (CME), caveolin-mediated and clathrin–caveolin-independent endocytosis. CME has been reported as the central route adopted by various ADCs. Sung and colleagues have described that N87-TM cells made resistant to T-DM1 internalize trastuzumab-ADCs into caveolin-1 (CAV1)-coated vesicles.

Impaired lysosomal function

ADCs need to reach the lysosomes, where the cytotoxic agent is released by chemical or enzymatic cleavage. In cells made resistant to T-DM1 by prolonged exposure to the drug, lysosomal accumulation of T-DM1 has been observed. In these cells, the drug reached the lysosomal compartment, but the proteolytic activity was below that present in sensitive cells. Such deficiency was due to increased lysosomal pH, which in turn inhibited lysosomal proteolytic enzymes. In theory, all ADCs in which lysosomal acidic proteases play a role in the degradation of the ADC could be exposed to this mechanism of resistance.

Drug efflux pumps

A common mechanism of resistance for chemotherapies is the elimination of the agent from the cellular cytoplasm by the ATP-binding cassette (ABC) transporters. These drug efflux pumps might also contribute to resistance to ADCs because many of the cytotoxic agents are substrates of ABC transporters.

Alterations in the target

A potential mechanism of resistance to ADCs could be mutations in the cellular target for the cytotoxic agent.

Role of cell cycle

One mechanism of resistance to T-DM1 recently proposed relates to the effect of the drug on cyclin B, a cell-cycle protein that participates in G2–M transition. In HER2þ breast cancer cells sensitive to T-DM1, the drug causes an increase in cyclin B, whereas in cells made resistant to T-DM1, such an increase was not observed. Moreover, the silencing of cyclin B resulted in resistance to the drug. Interestingly, in a patient cohort of 18 HER2+ breast cancer fresh explants, the antitumor action of T-DM1 paralleled cyclin B accumulation. These findings are clinically relevant, as cyclin B induction could be used to mark T-DM1 sensitivity.

Activation of signaling pathways

Activation of downstream signalling pathways may contribute to the acquisition of resistance to ADCs. Activated PI3K/AKT signalling has been associated with GO resistance in vitro in primary AML cells.

Apoptotic dysregulation

Changes in apoptotic regulation may also modulate sensitivity to ADCs. A role for the pro-apoptotic proteins BAX and BAK in the regulation of GO sensitivity in AML has been described previously. Furthermore, the overexpression of the antiapoptotic proteins BCL-2 and BCL-X has been linked to GO resistance.

FUTURE PERSPECTIVES OF ADC

The future of ADCs looks promising, with a growing number of ADCs entering clinical trials and new technological advances underway. In 2020, Trodelvy (sacituzumab govitecan), a third-generation ADC, was approved for triple-negative breast cancer (TNBC), demonstrating the potential for ADCs in treating cancers previously difficult to target. The approval of multiple ADCs in recent years has led to significant investments, such as Gilead's acquisition of Immunomedics for $21 billion. ADCs are also being explored for use in autoimmune diseases, such as rheumatoid arthritis, with companies like Allergan investigating anti-TNF ADCs for non-oncology indications.

CONCLUSION

Antibody-drug conjugates (ADCs) are a class of targeted therapies that combine chemotherapy with a monoclonal antibody (mAb) to deliver potent cytotoxic agents directly to cancer cells, enhancing the precision of treatment. ADCs are typically employed when cancer recurs, becomes resistant to other therapies, or metastasizes. While ADCs do not cure cancer, clinical evidence demonstrates that they can extend survival and improve outcomes for patients with certain blood cancers and solid tumors. In conclusion, the ADC field continues to evolve, offering significant therapeutic potential for both oncological and non-oncological applications. As research and development progress, ADCs are likely to play an increasingly important role in the treatment of cancer, providing a targeted, effective, and safer alternative to conventional chemotherapy.

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