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ADC – ANTIBODY-DRUG CONJUGATES IN ONCOLOGY

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ABSTRACT

Background: Antibody-drug conjugates (ADC) are a promising novel therapy for oncology patients as it combines tumor-targeted antibodies with cytotoxic molecules resulting in improved therapeutic outcomes.
Aim: The aim of this article is a thorough analysis of ADC possibilities in oncology focusing on treatment options, side effects of therapies for breast, bladder and lung cancers.
Material and methods: A search of relevant research databases was conducted to identify eligible papers.
Results: Findings reveal ADC to be a promising treatment option as a innovative, more precise form of therapy.

KEYWORDS

Antibody-drug Conjugates, Breast Cancer, Bladder Cancer, Lung Cancer

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1. Introduction

Antibody-drug conjugates (ADCs) were first introduced in the late 1980s and since then four generations of the drug have been developed (1). ADC are a promising novel therapy for oncology patients as it combines tumor- targeted antibodies with cytotoxic molecules resulting in improved therapeutic outcomes (2).

ADCs can be classified according to their structure and properties. The first generation of ADCs to be developed was comprised of cytotoxic agents conjugated with mouse monoclonal antibodies, which often led to immune reactions, thereby reducing their efficacy and safety. Therefore, the combination was replaced by humanized monoclonal antibodies. These molecules were hydrophobic in nature and tended to aggregate, which shortened their half-life in the bloodstream. The second generation of ADCs used fully human monoclonal antibodies and more potent cytotoxic agents, which improved the therapeutic ratio. Third-generation ADCs were developed to improve the efficiency and selectivity of drug conjugation. Toxicity and immunogenicity were reduced, and the combination demonstrated better compatibility. Additionally, the third generation contained hydrophilic linkers which prolong their presence in the bloodstream. Fourth-generation ADCs include, amongst others, trastuzumab deruxtecan and sacituzumab govitecan, which exhibit even greater cytotoxicity in tumor cells. All these modifications are aimed at increasing cytotoxicity in tumour tissues and thereby enhancing their efficacy in treatment (3).

2. Research materials methods

This systematic review aimed at summarizing the most meaningful and current information on the topic of prebiotics and probiotics implementation as a therapeutic method in SIBO. The research was carried out using search phrases in PubMed. Those phrases included: “ADC” and “ADC – Antibody-Drug Conjugates in oncology”.

3. Results

3.1 The mechanism of action

The mechanism of action of ADCs starts with the binding of the antibody component to a surface antigen expressed by the cancer cell. Following formation of the antigen–ADC complex, the conjugate is internalized by endocytosis and transported to the endosomal and lysosomal compartments (4, 5).

After internalization, the payload is released within the cell. Depending on the design of the ADC, this can occur through cleavage of the linker or degradation of the antibody component in the lysosome (5).

Once released, the cytotoxic payload acts on its intracellular target. Its effects depend on the payload used and may include inhibition of microtubule polymerization, inhibition of topoisomerase I, or induction of DNA damage. These effects ultimately interfere with cellular proliferation and lead to cancer cell death (4, 6).

The linker type is an important determinant of ADC effect. Cleavable linkers facilitate payload release under specific intracellular conditions, whereas non-cleavable linkers generally depend on degradation of the antibody component within the lysosome (7, 8).

Linker and payload properties additionally affect the likelihood of a bystander effect. The bystander effect refers to the ability of the released payload to affect not just the cell that has internalised the ADC, but also nearby tumor cells. This phenomenon is especially important in tumours characterised by heterogeneous antigen expression, where some cells exhibit high antigen expression, while others have low levels or none at all. If the released payload can penetrate cell membranes, it can leave the target cell and enter neighbouring cells, inducing a cytotoxic effect. As a result, the bystander effect may enhance therapeutic efficacy by allowing ADCs to affect tumour cells that do not directly express the target antigen. This mechanism may be particularly relevant for ADCs such as trastuzumab deruxtecan (T-DXd), which contains a membrane-permeable payload capable of reaching neighbouring cells (9-11).

However, greater payload diffusion may also expose neighbouring normal cells to the cytotoxic agent. The bystander effect can therefore influence both the efficacy and safety of ADC treatment (9, 11).

Overall, ADC efficacy results from the combination of selective tumor-cell recognition by the antibody and the potent cytotoxic activity of the payload. The bystander effect can further contribute to antitumor activity, particularly in tumors with heterogeneous antigen expression. Its occurrence and extent are influenced largely by the properties of the linker and payload.

3.2 Side effects of the therapy

Despite the considerable progress achieved with ADCs in targeted cancer therapy, their clinical application continues to be constrained by a relatively narrow therapeutic window, primarily owing to toxicity, structural limitations, and the development of drug resistance (3). One of the major biological challenges is the nonspecific uptake of ADCs by healthy tissues. This phenomenon may occur through several mechanisms, including the expression of the target antigen on normal cells, which can result in on-target, off-tumor toxicity. In addition, ADCs may be internalized through fluid-phase pinocytosis or interact with Fc receptors, such as FcγR and FcRn, expressed by cells of the reticuloendothelial system (12).

The bystander effect represents another mechanism with a dual therapeutic significance. Although the diffusion of the released cytotoxic payload into neighboring cells can improve the treatment of tumors with heterogeneous antigen expression, it may simultaneously increase damage to surrounding healthy tissues when the payload reaches nonmalignant cells (12).

The pharmacological behavior and toxicity profile of ADCs are also strongly influenced by the chemical characteristics of the linker and the drug-to-antibody ratio (DAR) (13). Insufficient linker stability in the systemic circulation, together with an excessively high DAR, may increase the hydrophobicity of the conjugate. Such changes can promote premature hepatic clearance and facilitate the uncontrolled release of the cytotoxic payload into the bloodstream, thereby contributing to off-target toxicity (13) (14).

The nature of adverse effects associated with ADC therapy is largely determined by the pharmacological mechanism of the conjugated payload. ADCs incorporating microtubule inhibitors, including MMAE and DM1, are predominantly associated with severe neutropenia, peripheral sensory neuropathy, and ocular adverse effects, such as microcystic corneal changes. In comparison, ADCs carrying topoisomerase I inhibitors, such as DXd and SN-38, are more frequently associated with interstitial lung disease (ILD) and gastrointestinal toxicity (15). The occurrence and severity of these adverse events may necessitate therapeutic modifications, including dose reduction or treatment discontinuation, as well as the implementation of appropriate preventive or supportive measures (15).

The effectiveness of ADC-based therapy may additionally be compromised by physical barriers within the tumor microenvironment. Due to their relatively large molecular size, immunoglobulin-based therapeutics may exhibit limited penetration into the deeper regions of solid tumors, potentially reducing the uniform distribution of the drug within the tumor mass (14). Furthermore, acquired resistance constitutes an important mechanism of therapeutic failure. It may arise from mutations or reduced expression of the target antigen, impaired endocytosis and internalization of the ADC–antigen complex, or enhanced intracellular efflux of the cytotoxic payload mediated by ATP-binding cassette (ABC) transporters, including MDR1/P-glycoprotein (P-gp) (14).

3.3 Breast cancer

Breast cancer is the leading cause of cancer deaths in women around the world(16). This disease is treated by a wide variety of methods, including surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, and immune therapy. Furthermore, breast cancer represents a pioneering and one of the most dynamic areas of use for ADCs in solid tumor oncology. Thanks to this therapeutic method, we can precisely deliver a highly potent cytotoxic payload directly into the tumor (17, 18). T-DM1 (trastuzumab emtansine) which is a first-generation conjugate, was a pioneer in this group. It links a monoclonal antibody targeting the HER2 receptor to a microtubule inhibitor (DM1) via a stable, non-cleavable thioether linker (18, 19). T-DM1 demonstrated high efficacy in patients with strong HER2 overexpression in the advanced setting as well as in post-neoadjuvant adjuvant treatment. However, its limitation is the lack of a strong bystander effect, which reduces therapeutic response in tumors with significant heterogeneous receptor expression(19).The introduction of second-generation molecules, such as trastuzumab deruxtecan (T-DXd) brought a therapeutic breakthrough. T-DXd features a high drug-to-antibody ratio, an enzymatically cleavable linker, and a highly lipophilic payload consisting of a topoisomerase I inhibitor (DXd) (17, 19). When released, the payload diffuses across cell membranes into adjacent tumor cells, destroying even those with low or absent target antigen expression (20). Furthermore, thanks to the ADC technology, scientists were able to progress in triple-negative breast cancer (TNBC), which is a subtype characterized by poor prognosis and a lack of traditional therapeutic targets. Sacituzumab govitecan (SG) targets the Trop-2 glycoprotein, which is overexpressed in more than 90% of TNBC cases (17, 18). By delivering an SN-38 payload with a DAR of ~7.6, scientists observe a significant improvement in progression-free survival and overall survival in the ASCENT trial, while also earning approval in resistant HR+/HER2- breast cancer(17).In summary, antibody-drug conjugates have significantly impacted the methods of treatment of breast cancer. Thanks to cleavable linkers, higher drug-to-antibody ratios, and the bystander, effect scientists were able to successfully address multiple clinical challenges, for example, tumor heterogeneity and drug resistance(17, 18). This proves that ADCs should be further investigated to efficiently treat breast cancer.

3.4 Bladder and lung cancer

Each year, more than half a million people are diagnosed with bladder cancer. When detected early, the disease has a high survival rate, which underscores the importance of diagnosing it before the tumor becomes muscle-invasive. Histologically, the vast majority of cases are urothelial carcinomas (21).

ADCs have the potential to improve the prognosis for patients with bladder cancer, especially those with advanced-stage disease who experience recurrence or metastasis despite treatment with conventional therapies – surgery, chemotherapy, and radiation therapy (22).

The primary molecular targets of ADCs are bladder cancer-specific antigens – Nectin-4, HER2, and TROP2 (23).

Enfortumab vedotin (anti-Nectin-4) has been shown to extend OS in patients with advanced bladder cancer to 12.9 months, compared with 9 months for standard chemotherapy (platinum and PD-1 inhibitor therapy) (24).

Sacituzumab govitecan (anti-TROP2) demonstrated an ORR of 27% among patients whose cancer had progressed despite platinum-based chemotherapy (25).

Disitamab vedotin (anti-HER2) demonstrates promising anticancer activity in HER2-positive tumors, while maintaining a good safety profile (26).

In 2022, approximately 2.5 million cases of lung cancer were diagnosed. It remains the leading cause of cancer death. The traditional classification includes non-small-cell lung cancer (NSCLC), which accounts for about 85% of cases, and small-cell lung cancer (27).

Currently, there are three FDA-approved ADC drugs for the treatment of NSCLC in previously treated patients with advanced-stage disease: trastuzumab deruxtecan, datopotamab deruxtecan, and telisotuzumab vedotin (28).

HER2 mutations affect only about 2% of patients with NSCLC and are associated with a poor prognosis (29). In the DESTINY-Lung01 trial, trastuzumab deruxtecan (anti-HER2) at a dose of 6.4 mg/kg achieved an ORR of 55%; unfortunately, 26% of patients developed interstitial lung disease (ILD) (30). In the DESTINY-Lung02 trial, a dose of 5.4 mg/kg achieved an ORR of 49% while reducing the incidence of ILD to 13% (31).

The NCCN recommends datopotamab deruxtecan (anti-TROP2) as the preferred drug for subsequent therapy in patients with EGFR mutations (28). In a pooled analysis of the Phase II TROPION-Lung05 and Phase III randomized TROPION-Lung01 trials, the ORR was 43%, and the median OS was 15.6 months (32).

The efficacy of telisotuzumab vedotin (anti-c-Met) was demonstrated in the LUMINOSITY trial among patients with nonsquamous EGFR wild-type NSCLC and c-Met overexpression. Among patients with overexpression >50%, the ORR was 34.6%, and the median OS was 14.6 months (33).

3.5 Hematooncology

ADCs have been identified as a turning point in pharmacotherapy for hematologic oncology. Hematological malignancies are an optimal environment for this kind of drug due to the repeated expression of target antigens on their surface and the easy access of ADCs to cancer cells, even with large molecular weight (34). Some of the targets for ADCs are focused on because they are homogeneously and broadly expressed at higher levels on malignant hematological cells. Those biomarkers are mainly CD19, CD20, CD22, CD30, CD33, BCMA (B-cell maturation antigen), and CD79 (35).

CD19 (the B-cell transmembrane glycoprotein) Expression starts on B cells at the pro-B cell stage and is present until the cell is mature and enters activation stages (36). This receptor is recognized by a humanized anti-CD19 IgG1 antibody conjugated with a PBD dimer SG3199 (DNA - damaging agent), in Loncastuximab tesirine, which is FDA-approved for relapsed and refractory DLBCL. The LOTIS-2 phase 2 trial indicated that the drug has antitumor activity and induces a response with an acceptable safety profile (37, 38).

CD22 is part of the sialic acid-binding Ig-like lectin (Siglec) family and is a regulator of B-cell signaling; it takes part in the negative regulation of the B-cell receptor (BCR) (39). Its specific expression and absence on other non-B cell and HSCs made it an attractive transmembrane protein to target with ADC treatments (38). CD22 is targeted by two FDA-approved ADCs; one of those is Moxetumomab pasudotox-tdfk, an antibody conjugated with PE38 (protein toxin), in the treatment of Hairy Cell Leukemia in adults with relapsed or refractory HCL, who, for subsequent lines of treatment, have a significantly higher risk of relapse or adverse reactions (40, 41).

CD30 is a transmembrane glycoprotein receptor that is a member of the tumor necrosis factor receptor (TNFR) family. Its expression is relatively restricted to activated T cells, B cells, and natural killer (NK) cells; however, its overexpression can be seen in some lymphomas, such as Hodgkin and Reed-Sternberg cells of classical Hodgkin lymphoma, cutaneous T-cell lymphoma (CTCL), and anaplastic large cell lymphoma (ALCL). This means that the receptor can be selectively chosen as a treatment target. This approach is used by Brentuximab vedotin an antibody-drug conjugate with the payload MMAE (microtubule inhibitor). Despite selective ligand selection, treatment is dose-limited due to MMAE neuronal toxicity, which can lead to peripheral sensory and motor neuropathy (38, 42).

CD33 is a transmembrane glycoprotein, part of sialic acid-binding immunoglobulin-like lectin (SIGLEC), expressed on myeloid cell lineage and leukemic blasts, with higher expression in 85-90% of patients. This creates an opportunity for new ADC development. One FDA-approved ADC is Gemtuzumab ozogamicin, an antibody combined with Calicheamicin (DNA-damaging). The first trial in 2000 showed increased induction-related mortality, causing withdrawal. Then, the AML15 and AML16 trials showed that using gemtuzumab ozogamicin with changed dosing decreases the risk of relapse and improves 5-year overall survival (38, 43, 44).

CD79B participates in B-cell receptor (BCR) signaling and transduction through the plasma membrane. It is expressed only on B cells and B-cell neoplasms in 80-90% of cases (45). It is targeted by Polatuzumab vedotin-piiq conjugated with MMAE (microtubule inhibitor). It is used as part of the therapy along with bendamustine and rituximab (pola-BR treatment) in patients with transplantation-ineligible relapsed/refractory diffuse large B-cell lymphoma (DLBCL) . Those administered with pola-BR had a significantly higher CR rate 40.0% vs 17.5%; (pola-BR vs BR; P = .026) and longer PFS (median, 9.5 vs 3.7 months) than those administered only with bendamustine and rituximab (BR) (46). There are also some adverse effects; the most common are neutropenia, anemia, thrombocytopenia, and, most importantly, peripheral neuropathy – in the same way as described in the CD30 chapter with Brentuximab vedotin (43).

4. Conclusions

ADCs are a precise therapeutic tool allowing for the treatment of solid tumors including triple-negative breast cancer (TNBC), known for its poor prognosis and a lack of traditional therapeutic targets. Fuhermore, Bladder cancer which are usually found in later stages and are thus difficult to treat due to their metastatic nature are more likely to be treated fully by using ADCs with traditional treatments methods such as chemotherapy or surgery.

Future generations of ADCs with the addition of modern day technologies including AI, nanotechnology will further improve the targeting of the cancer treatments and optimize outcomes for patients (1).

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