Antibody–drug conjugates – the magic bullet?

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Summary Antibody–drug conjugates (ADCs) are a relatively new class of highly potent molecules which combine the targeting properties of monoclonal antibodies with the cell destructive properties of cytotoxic agents in order to reduce systemic exposure and toxicity of the latter. Gemtuzumab–ozogamicin was the first-in-class drug approved by the US Food and Drug Administration (FDA) in 2000, but later approval was withdrawn. In the meantime, the number of these types of drugs available for clinical use is rapidly evolving. This review gives a brief overview of currently approved ADCs, with special consideration of pharmaceutical aspects

Keywords Payload · Linker · Targeted therapy · In-use stability · Compounding

Introduction

Classic chemotherapy is based on the theory that cytotoxic agents, interfering in cell division at different timepoints, would destroy cancer cells, whereas healthy cells would not be harmed due to their lower division rate. Nevertheless, chemotherapy causes well-known toxicities and the search for targeted therapies with specific efficacy on tumor cells is not yet completed satisfactorily.

Already the Nobel laureate Paul Ehrlich (1854–1915) developed the idea of what he called “magic bullet” [1]: a therapeutic agent, which would be able to identify its target, without harming the body itself. He also anticipated the concept of attaching a toxin (e.g., ar-

senic) to an antibody to improve therapeutic specificity [2]. Based on this understanding, we are nowadays able to design a multitude of highly complex molecular structures.

Antibody–drug conjugates (ADCs) are molecules consisting of three components (Fig. 1), all of which are relevant for pharmacological properties of the drug.

Antibody

The antibody is responsible for the delivery of the cytotoxic agent to the tumor cells. It needs target specificity and high target-binding affinity. Furthermore, low immunogenicity is important [3].

Linker

The linker has the essential function to maintain the conjugate in an inactive, nontoxic state while circulating in the blood; it unleashes the cytotoxic drug upon internalization in the tumor cells. Its chemical properties determine how and when this release occurs and therefore determine whether the so-called bystander effect might occur, an unwanted toxic effect on surrounding healthy cells [4].

Noncleavable linkers provide higher stability and do not unleash the cytotoxic agent at off-target sites and therefore reduce toxicity. The only approved ADC with an uncleavable linker is trastuzumab–emtansine (T-DM1) [5].

Most of the clinically approved ADCs have cleavable linkers [6] which use the inherent properties of tumor cells to release the cytotoxin: β -glucuronidase richness in tumor necrotic regions, acidic tumor microenvironment, lysosomal proteases expressed by tumor cells, lower pH, elevated intracellular concentration of glutathione [7].

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Fig. 1 Schematic representation of antibody–drug conjugates (ADCs) and their mechanism of action. Clinical efficacy of ADCs is determined by fine-tuning combination of tumor antigen, targeting antibody, cytotoxic payload and conjugation strategy (a). ADC binds to tumor target cell surface antigens (b) leading to trigger a specific receptor mediated internalization (c). The internalized ADCs are decomposed to re-

lease cytotoxic payloads inside the tumor cell either through its linkage/linker sensitivity to protease, acidic, reductive agents or by lysosomal process, leading to cell death (d). Ab antibody. From: [24]. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). This figure is not included under the Creative Commons CC BY license of this publication.

All available drugs (Table 1) are formulated as a lyophilized powder, which needs reconstitution and further dilution upon infusion. In clinical routine, those compounding procedures are performed by pharmaceutical professionals; thus, interdisciplinary communication between treating physicians and responsible pharmacists is essential, especially due to short in-use shelf-life once the drug is reconstituted.

Chemical characteristics of the linkers are not only responsible for the in vivo activity of the compound, but also for its physicochemical shelf-life. Whereas trastuzumab–emtansine [8] has a chemically stable, noncleavable linker and therefore long in-use stability (e.g., 24 h), drugs with a cleavable linker are more prone to chemical instability. Examples include inotuzumab–ozogamicin [9] and sacituzumab–govitecan (SG) [10]—both of which are stable for only 4 h, once reconstituted. Degradation via hydrolysis, resulting in both increased toxicity and/or reduced efficacy, is the most likely effect assumable for low in-use stability time. This might also be the reason why most of the products require protection from light

from the beginning of reconstitution until end of application (e.g., trastuzumab–deruxtecan [11], gemtuzumab–ozogamicin [12]).

Payload

The cytotoxic payload becomes activated upon release from the ADC inside the cytoplasm of tumor cells. Essential properties are a small molecular weight and a long half-life.

Three principles of action are used in currently approved drugs:

- Microtubule-disrupting agents: auristatin, maytansinoids.
- DNA-alkylating agents: calicheamicins, pseudomonas exotoxin, pyrrolobenzodiazepine.
- Topoisomerase inhibitors: camptothecin derivatives.

Table 1 ADCs with FDA and/or EMA approval (as of October 5, 2021)

Drug	Trade name	Target	Payload	Condition
Gemtuzumab–ozogamicin [12]	Mylotarg®	CD33	Calicheamicin	Acute myeloid leukemia
Brentuximab–vedotin [18]	Adcetris®	CD30	Auristatin	Hodgkin lymphoma
Trastuzumab–emtansine [8]	Kadcyla®	HER2	Maytansine	Breast cancer
Inotuzumab–ozogamicin [9]	Besponsa®	CD22	Calicheamicin	Acute lymphoblastic leukemia
Polatuzumab–vedotin [19]	Polivy®	CD79B	Auristatin	Diffuse large B-cell lymphoma
Belantamab–mafodotin [20]	Blenrep®	BCMA	Auristatin	Multiple myeloma
Trastuzumab–deruxtecan [11]	Enhertu®	HER2	Exatecan	Breast cancer
Sacituzumab–govitecan [10]	Trodely®	Trop-2	SN-38	Breast cancer, Bladder cancer
Enfortumab–vedotin [21]	Padcev®	Nectin-4	Auristatin	Urothelial cancer
Moxetumumab–pasudotox [22]	Lumoxiti® (EMA approval withdrawn—July 2021)	CD22	PE38 (pseudomonas exotoxin A)	Hairy cell leukemia
Loncastuximab–tesirine [23]	Zynlonta®	CD19	Pyrrolobenzodiazepine	Diffuse large B-cell lymphoma

ADC antibody–drug conjugates, FDA US Food and Drug Administration, EMA European Medicines Agency

Drug–drug interactions

Cytochrome P450 with all its subtypes, especially CYP3A, plays a significant role in the metabolism of drugs. With auristatin [13] and maytansine [14] being metabolized via CYP3A4, the expectation would be significant interaction between ADCs containing these payloads and strong inhibitors or inducers. Even though these effects may be seen in *in vitro* investigations, no clinically significant changes in plasma levels are observed. One possible explanation could be the small amount of payload circulating in plasma, which is in line with the mechanism of the linker releasing the payload only upon cellular internalization.

This also applies for SN-38, a substrate of UDP-glucuronyltransferase (UGT1A) [15] which also underlies inducing and inhibiting alterations, for instance, through phenytoin and ciclosporin, respectively.

However, in order to provide subjects with best possible precautions, pharmaceutical counselling or drug–drug interaction (DDI) checks should be performed before any change of systemic oncological treatment [16].

Regarding toxicity management, it is worth noting that the cytotoxic payload of the conjugate might have a different safety profile than its equivalent used as classical chemotherapy. As an example, the emetogenic risk of the camptothecin derivatives shall be mentioned: whereas irinotecan (including its active metabolite SN-38) and topotecan are usually classified as having low-to-moderate risk, sacituzumab–govitecan and trastuzumab–deruxtecan are of moderate-to-high risk [17].

To summarize, with newly developed antibodies, linkers and payloads, ADCs represent an interesting extension of medical oncological treatment options, which is an advancement of medicine toward Ehrlich's vision of magic bullets in clinical practice.

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Conflict of interest M.-B. Aretin declares that she has no competing interests.

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