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Antibody-drug conjugates: Current status and future perspectives

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ABSTRACT

Conventional cytotoxic agents used for the pharmacotherapy of cancer do not selectively localize at the tumor site, which may prevent dose escalation to therapeutically active regimens and may lead to undesired side effects and toxicity to normal organs. There has been a growing interest in the use of monoclonal antibodies as vehicles for the pharmacodelivery of potent cytotoxic drugs to neoplastic lesions. This novel class of targeted biopharmaceutical agents has the potential of improving activity and selectivity of cytotoxic agents. However, many technical aspects contribute to the success or failure of antibody-drug conjugates (ADCs). In this review, we summarize important pre-clinical and clinical examples of early and current improvements in the field ADCs, including diversification of payloads, linkers, conjugation technologies, ADC formats and type of targets. Combination therapies of ADCs with checkpoint inhibitors are also discussed, in light of the exceptional expansion recorded in the latter space over the last five years.

1. Introduction

Chemotherapy represents an essential pillar for the treatment of various forms of cancer. However, cytotoxic agents (and, more in general, small molecule anti-cancer drugs, including tyrosine kinase inhibitors) do not preferentially accumulate in tumors both in animal models and in patients (van der Veldt et al., 2010; Krall et al., 2013; van der Veldt et al., 2013). This limitation may prevent dose escalation to therapeutically active regimens and may cause undesired toxicities. For this reason, substantial efforts are devoted to the development of therapeutic strategies, which facilitate the selective delivery of bioactive payloads at sites of disease. Historically, antibodies have always been considered as ideal pharmacodelivery vehicles, because of their exquisite binding specificity to the cognate antigens. Some tumor-targeting antibodies have demonstrated an impressive ability to selectively localize at neoplastic sites in mouse models of cancer and in patients (Neri & Bicknell, 2005; Knowles & Wu, 2012; Larson et al., 2015).

With some exceptions, unnmodified mAbs have a limited curative potential for cancer treatment, often displaying only incremental activity over other forms of pharmacotherapy (Carter, 2001; Wu & Senter, 2005; Gurcan et al., 2009). Efforts have been made to enhance the complement dependent toxicity and antibody-dependent cell-mediated cytotoxicity, which are believed to be extremely important components of the therapeutic activity of anti-cancer antibodies. Indeed, promising results have been achieved by mutagenesis of the Fc portion or by glycosylation engineering of therapeutic antibodies (Kellner et al., 2014). More recently, there has been a substantial clinical and industrial interest on immunological checkpoint inhibitor blockade, which has led to the approval of antibody products targeting CTLA-4 (Ipilimumab™), PD1 (Nivolumab™ and Pembrolizumab™) and PD-L1 (Atezolizumab™). At present, there are at least 70 PD1/PDL1 preclinical and clinical programs. Pembolizumab alone is currently being used (alone or in combination) in more than three hundred clinical studies. These mAbs release the inhibition brake of T-cells, thus activating the immune system (Parry et al., 2005; Postow et al., 2015).

Over the last two decades, there have been many academic and industrial efforts, aimed at arming antibodies with drugs, cytokines, toxins and radionuclides (Hess et al., 2014). The possibility to combine the favorable binding properties of mAbs with the biocidal activity of potent cytotoxic agents promises to increase the therapeutic index of therapeutic payloads (Chari, 2008; Panowksi et al., 2014). The concept of using antibodies for drug delivery is old (Ghose & Blair, 1978), but the successful implementation of antibodies, linking strategies and payloads into a therapeutically effective product remains an art [Fig. 1]. At present, only two ADC products hold a marketing authorization for the therapy of certain types of cancer: Adcetris™ (Senter & Sievers, 2012) and Kadcyla™ (Ballantyne & Dhillon, 2013) [Fig. 2].

ADC development was not an easy "one-step" story. Initial attempts, using approved drugs with suitable structural features, allowing their conjugation to antibody molecules, suffered from a series of shortcomings. BR96-doxorubicin is an example of a first generation ADC (Trail et al., 1993), in which a chimeric mAb (BR96), directed against

Abbreviations: ADCs, antibody-drug-conjugates; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; B-NHL, B-cell non-Hodgkin's lymphoma; ccRCC, clear cell renal cell carcinoma; DLBCL, diffuse large B-cell lymphoma; DAR, drug to antibody ratio; ECM, extra cellular matrix; GO, Gemtuzumab ozogamicin; IgG, Immunoglobulin G; mAb, monoclonal antibody; MDR, multidrug resistance; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PBD, pyrrolobenzodiazepines.

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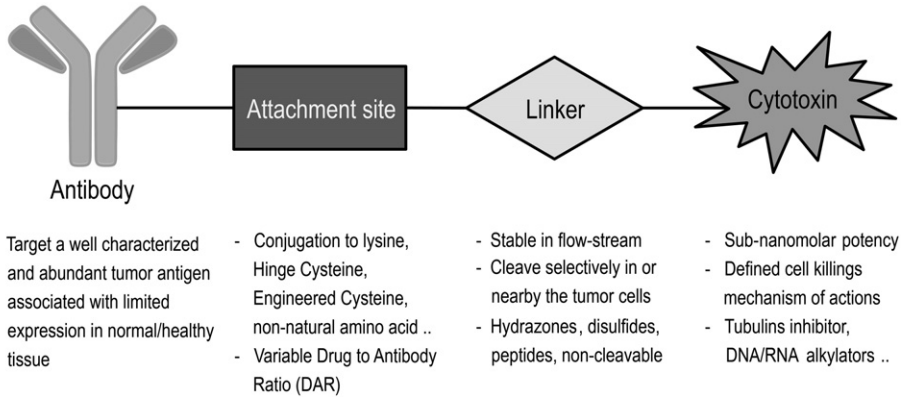

Fig 1. Key component of an ADC.

the LewisY tetrasaccharide (LeY) antigen commonly expressed on human carcinomas, was linked to eight molecules of doxorubicin, a clinically approved DNA intercalator. The drug was coupled to the hinge cysteine residues of BR96 by an acid-labile hydrazone linker (Dubowchik & Walker, 1999). Upon binding to cell surface antigens and internalization, the acidic environment (approx. pH = 5) found in endolysosomal compartments would trigger a selective doxorubicin release from the conjugate. In preclinical studies, both tumor bearing mice and rats were successfully cured from cancer, although at doses as high as 100 mg/kg, possibly reflecting the low potency of the payload used. A phase I clinical trial showed the ability of the conjugate to deliver doxorubicin to the tumor cells, although dose-limiting toxicities were observed with injections every 3 weeks of 700 mg/m^2 of the product (Saleh et al., 2000). A subsequent randomized Phase II trial on a population with confirmed sensitivity to doxorubicin revealed that the toxicity might have been of gastrointestinal origin, due to normal gut expression of LeY antigen (Tolcher et al., 1999). In both clinical trials, low antitumor activity was observed. Furthermore, the discrepancy between the long circulation half-life of full IgG (approximately 12 days) and the short half-life of the hydrazone linker (43 h) represented a cause of concern for undesired toxicity, due to premature off-target drug release.

These initial results highlighted critical issues in first generation ADCs. Today, a growing number of parameters can be engineered into novel ADCs, including drug potency, careful target selection and appropriate linker stability.

2. Payloads

The payloads employed in the first generation of ADCs (e.g. those based on doxorubicin) were "penalized" by the fairly low accumulation of antibody at tumor sites after intravenous administration. While in mice good tumor-targeting antibodies may exhibit an uptake in the neoplastic mass corresponding to 10–50% injected dose per gram of tumor, in patients the best antibodies may reach 0.01–0.1% injected dose per gram of tumor mass (Sedlacek, 1992; Wong et al., 1997; Ychou et al., 1998; Lee et al., 2001; Stillebroer et al., 2012; Heuveling et al., 2013). For this reason, the focus of drug developers progressively moved towards the use of potent drugs, capable of killing cells at subnanomolar concentrations (Chari et al., 2014). In principle, various types of cytotoxic drugs could be considered, which exploit different modes of action. They can be subdivided into three main categories, corresponding to distinct intracellular targets: tubulin filaments, DNA and RNA [Fig. 3].

2.1. Tubulin filaments

The two most widely used drug platforms for ADC development are based on maytansinoids or auristatins. These payloads represent the cytotoxic moieties of two FDA-approved ADCs: ADCETRIS™ [auristatin: MMAE, free drug display IC_{50} = 0.01–0.1 nM] (de Claro et al., 2012) and KADCYLA™ [maytansinoid: DM1; alkylated derivatives display IC_{50} = 0.01–0.04 nM] (Krop & Winer, 2014). Both types of payloads

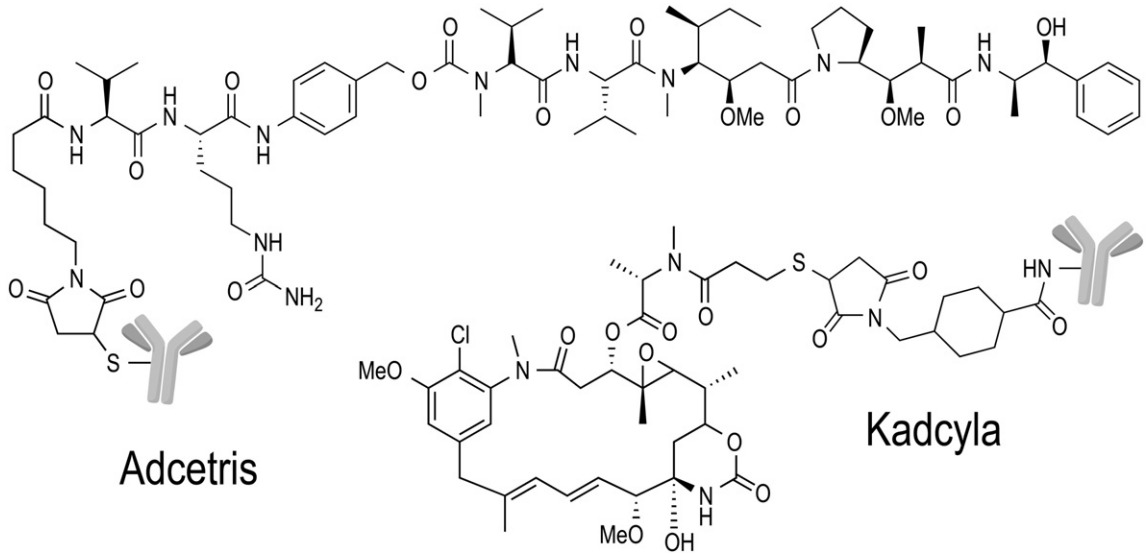

Fig 2. Structure of the two clinical approved ADCs: Adcetris™ (Bretuximab vedotin) and Kadcyla™ (Trastuzumab emtansine).