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New developments for antibody-drug conjugate-based therapeutic approaches

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The clinical success of Adcetris® (brentuximab vedotin) and Kadcyla® (ado-trastuzumab emtansine) has sparked clinical development of novel ADCs. These powerful anti-cancer agents are designed to allow specific targeting of highly potent cytotoxic agents to tumor cells while sparing healthy tissues. Despite the use of tumor-specific antibodies, the emerging clinical data with ADCs indicates that adverse effects frequently occur before ADCs have reached their optimal therapeutic dose, resulting in a relatively narrow therapeutic window. This review summarizes the therapeutic window of ADCs currently in clinical development, along with some strategies that may help to widen the window.

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Introduction

The prospects for development of antibody-drug conjugates (ADCs) as effective, well-tolerated anti-cancer therapeutics have changed dramatically since the approval of Adcetris® (brentuximab vedotin) in 2011 and Kadcyla® (ado-trastuzumab emtansine) in 2013. Currently, over 50 different ADCs are in clinical development, the majority consisting of IgG1 antibodies conjugated with potent microtubule inhibitors, either derivatives of maytansine, or auristatins which are analogs of dolastatin 10 (Table 1). These compounds display cytotoxicity at ~1000-fold lower concentration than standard chemotherapeutic agents [1], which makes them too toxic for systemic treatment [2,3]. By conjugating these potent cytotoxins to tumor-specific antibodies, their cytotoxic effect can be concentrated at tumor cells. At the same time, the pharmacokinetic profile of the toxins will improve upon conjugation to antibodies, giving to the small molecular weight cytotoxin the long half-life of an immunoglobulin. Notwithstanding the clinical success of brentuximab vedotin and ado-trastuzumab emtansine, the development for therapeutic use of most ADCs is still hampered by a relatively narrow therapeutic window. Although tumor-specific antibodies allow enrichment of cytotoxic payloads in tumors, adverse effects frequently occur before ADCs have reached their optimal therapeutic dose, which may limit their clinical response. In this short review, we have summarized available data from clinical and preclinical studies to assess the therapeutic window of ADCs. In addition, this review will discuss three aspects of ADC design, that may be important factors in helping to increase the therapeutic window of ADCs (Figure 1): first, the target selection requirements for ADC development; second, the interaction of ADCs with the immune system; third, the development of novel DNA damaging agents with low picomolar efficacy.

Therapeutic window of ADCs in clinical development

The majority of ADCs in clinical development make use of tubulin-targeting antimitotic agents. These agents (maytansinoids and auristatins [4]) bind to the vinca-binding domain of tubulin, thereby interfering with microtubule dynamics and causing cell cycle arrest in the G2/M phase [5]. Table 1 shows that antibodies coupled with the maytansinoids DM1 or DM4 typically reach a maximum tolerated dose (MTD) in humans in the range of 110–240 mg/m^2 (about 3–6.5 mg/kg) [6–8]. For antibodies conjugated with the dolastatin 10 analogs, monomethyl auristatin E or F (MMAE; MMAF), MTDs were established at doses around 80–110 mg/m^2 (about 2–3 mg/kg) [9–11]. It is not known what dose would be required to achieve optimal therapeutic efficacy in the clinic. However, some lessons may be drawn from preclinical studies in murine xenograft models. Given that both mice and humans have about 40–43 mL plasma per kg of body weight [12], and assuming that pharmacokinetic properties are approximately similar in mice and human, therapeutic activity should be observed at similar dose levels in mice and human. Thus, ADCs conjugated with maytansinoids or auristatins should show preclinical activity at doses at or below 3–6.5 mg/kg and 2–3 mg/kg, respectively. Preclinical studies in mice suggest that such doses levels are often suboptimal. For example, ado-trastuzumab emtansine has an MTD of 3.6 mg/kg in humans [6]. In preclinical models of breast cancer, ado-trastuzumab

Table 1

Overview of ADCs in clinical development. The last column shows the maximum tolerated dose in mg/kg, as well as the reported dose-limiting toxicities

Drug names	Sponsor	Phase	Indication	Target	Payload	Linker	Bystander	MTD mg/kg
Adcetris, brentuximab vedotin, SGN-35	Seattle Genetics, Inc.	Approved	Hematological	CD30	MMAE	VC	Yes	1.8 [9] thrombocytopenia, neutropenia
Kadcyla, T-DM1, trastuzumab emtansine, PRO132365	Genentech, Inc.	Approved	Solid	HER2	DM1	SMCC	No	3.6 [6] thrombocytopenia, neutropenia
Inotuzumab ozogamicin, CMC-544	Pfizer	3	Hematological	CD22	Calicheamicin	Hydrazone acetyl butyrate	Yes	0.05 [52] thrombocytopenia, neutropenia
Gemtuzumab ozogamicin	Pfizer	2	Hematological	CD33	Calicheamicin	Hydrazone Acetyl Butyrate	Yes	0.25 [53,54] no DLT[a]
ABT-414	Abbvie	2	Solid	EGFR	MMAF	MC	No	3.0 [55] ocular toxicity
Glembatumumab vedotin, CDX-011, CR011-vcMMAE	Celldex therapeutics	2	Solid	gpNMB	MMAE	VC	Yes	1.9 [16] neutropenia, rash
IMMU-130, labetuzumab govitecan, labetuzumab-SN-38, hMN14-SN38	Immunomedics, Inc.	2	Solid	CEACAM5	SN-38	CL2A	Yes	6–10 [56] neutropenia, typhlitis, nausea
IMMU-132, sacituzumab govitecan, hrS7-SN-38	Immunomedics, Inc.	2	Solid	TROP2, EGP1	SN-38	CL2A	Yes	8–10 [57] neutropenia
Lifastuzumab vedotin, NaPi2b ADC, RG7599, DNIB0600A	Genentech, Inc.	2	Solid	NaPi2b	MMAE	VC	Yes	2.4 [26] dyspnea
Indusatumab vedotin, MLN0264, 5F9-vcMMAE	Millennium Pharmaceuticals, Inc.	2	Solid	GCC	MMAE	VC	Yes	1.8 [10] neutropenia
Polatuzumab vedotin, RG7596, DCDS4501A	Genentech, Inc.	2	Hematological	CD79b	MMAE	VC	Yes	2.4 [29] neutropenia
Pinatuzumab vedotin, RG7593, DCDT2980S	Genentech, Inc.	2	Hematological	CD22	MMAE	VC	Yes	2.4 [28] neutropenia
PSMA ADC	Progenics Pharmaceuticals, Inc	2	Solid	PSMA	MMAE	VC	Yes	2.5 [25] neutropenia, liver toxicity
SAR3419, coltuximab ravtansine	ImmunoGen, Inc.	2	Hematological	CD19	DM4	SPDB	Yes	4.3 [7] ocular toxicity
BMS-986148	Bristol-Myers Squibb	1, 2	Solid	MSLN	Unknown	Unknown	Unknown	
BT-062, Indatuximab ravtansine	Biotest Pharmaceuticals Corporation	1, 2	Hematological	CD138, Syndecan1	DM4	SPDB	Yes	2.7 [58] mucositis, anemia
IMMU-110, milatuzumab doxorubicin, hLL1-DOX	Immunomedics, Inc.	1, 2	Hematological	CD74	Doxorubicin	Hydrazone	Yes	>16 [59] no DLT reported

Table 1 (*Continued*)

Drug names	Sponsor	Phase	Indication	Target	Payload	Linker	Bystander	MTD mg/kg
MLN2704	Millennium Pharmaceuticals, Inc	1, 2	Solid	PSMA	DM1	SPP	Yes	No MTD reported neutropenia, neuropathy [60]
SAR408701	Sanofi	1, 2	Solid	CEACAM5	DM4	SPDB	Yes	
SC16LD6.5, rovalpituzumab tesirine	Stem CentRx, Inc.	1, 2	Solid	Delta-like protein 3 (DLL3)	D6.5 (PBD)	VA	Yes	0.2 [49,50•] thrombocytopenia, capillary leak syndrome
ABBV-399	Abbvie	1	Solid	Unknown	Unknown	Unknown	Unknown	
AGS-16C3F	Astellas Pharma Inc.; Agensys, Inc.	1	Solid	ENPP3	MMAF	MC	No	1.8 [23] ocular toxicity, thrombocytopenia
ASG-22ME	Astellas Pharma Inc.; Agensys, Inc.	1	Solid	Nectin4	MMAE	VC	Yes	
AGS67E	Agensys, Inc.	1	Hematological	CD37	MMAE	VC	Yes	
AMG 172	Amgen	1	Solid	CD27	DM1	Non-cleavable	No	
AMG 595	Amgen	1	Solid	EGFRvIII	DM1	SMCC	No	
AGS-15E	Agensys, Inc.	1	Solid	SLTRK6	MMAE	VC	Yes	
BAY1129980	Bayer	1	Solid	C4.4a	Unknown	Unknown	Unknown	
BAY1187982	Bayer	1	Solid	FGFR2	Unknown	Unknown	Unknown	
BAY94-9343, anetumab ravtansine	Bayer	1	Solid	Mesothelin	DM4	SPDB	Yes	6.5 [22] ocular toxicity
GSK2857916	GlaxoSmithKline	1	Hematological	BCMA	MMAF	MC	No	
Humax-TF-ADC, tisotumab vedotin	Genmab	1	Solid	TF	MMAE	VC	Yes	TBD [61]
IMGN289	ImmunoGen, Inc.	1	Solid	EGFR	DM1	SMCC	No	
IMGN529	ImmunoGen, Inc.	1	Hematological	CD37	DM1	SMCC	No	
IMGN853, mirvetuximab soravtansine	ImmunoGen, Inc.	1	Solid	FOLR1	DM4	Sulfo-SPDB	Yes	6.0 ocular toxicity [21]
LOP628	Novartis Pharmaceuticals	1	Solid	cKIT	Maytansine	Non-cleavable	No	
PCA062	Novartis Pharmaceuticals	1	Solid	p-Cadherin	Unknown	Unknown	Unknown	
MDX-1203, BMS936561	Bristol-Myers Squibb	1	Solid	CD70	Duocarmycin	VC	Yes	No MTD reported, neuropathy at 15 mg/kg [62]
MEDI-547, MI-CP177	Medimmune LLC	1	Solid	EphA2	MMAF	MC	No	
PF-06263507	Pfizer	1	Solid	5T4	MMAF	MC	No	
PF-06647020	Pfizer	1	Solid	Unknown	Unknown	Unknown	Unknown	
PF-06647263	Pfizer	1	Solid	EphrinA	Calicheamicin	Hydrazone acetyl butyrate	Yes	
PF-06664178	Pfizer	1	Solid	Trop-2	Microtubule inhibitor	Unknown	Unknown	
RG7450, DSTP3086S	Genentech, Inc.	1	Solid	STEAP1	MMAE	VC	Yes	2.4 [63] liver toxicity
RG7458, DMUC5754A	Genentech, Inc.	1	Solid	MUC16	MMAE	VC	Yes	2.4 [27] neutropenia
RG7598, DFRF4539A	Genentech, Inc.	1	Hematological	Unknown	MMAE	Unknown	Unknown	
SAR566658	Sanofi	1	Solid	CA6	DM4	SPDB	Yes	6.5 [64] ocular toxicity, diarrhea
SGN-CD19A	Seattle Genetics, Inc.	1	Hematological	CD19	MMAF	MC	No	Not yet reached at 6 mg/kg
SGN-CD33A	Seattle Genetics, Inc.	1	Hematological	CD33	PBD	VA	Yes	Neutropenia

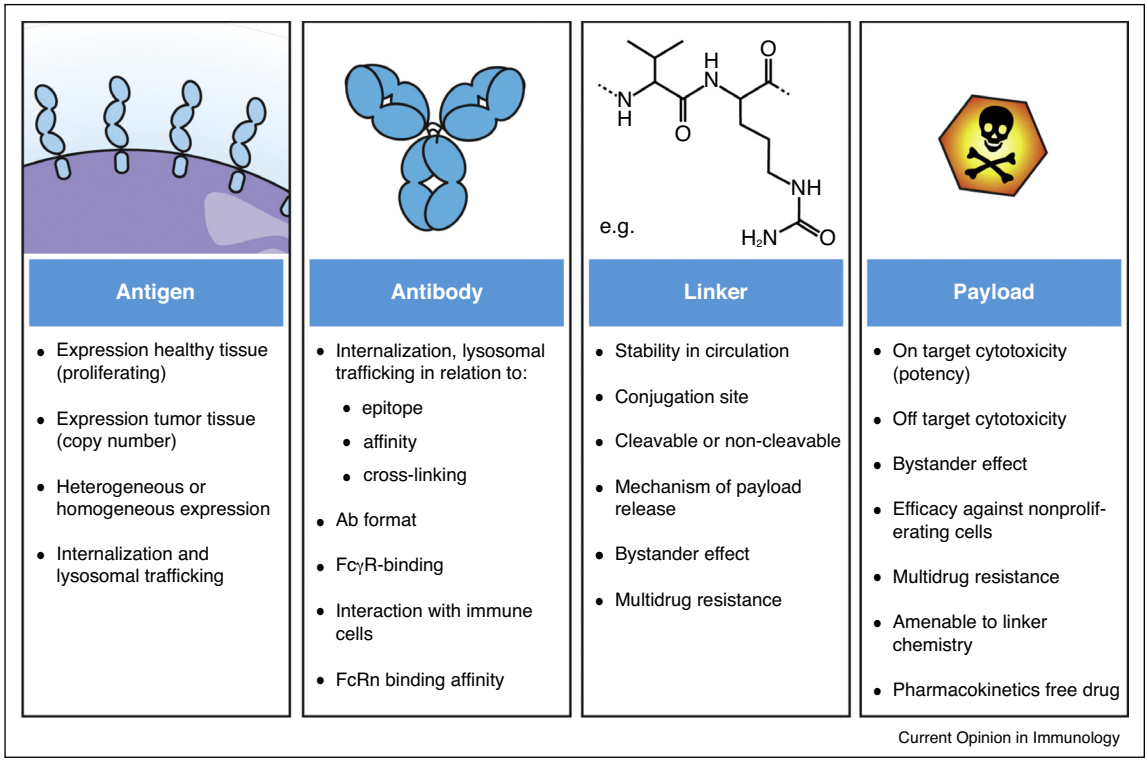
Table 1 (*Continued*)

Drug names	Sponsor	Phase	Indication	Target	Payload	Linker	Bystander	MTD mg/kg
SGN-CD70A	Seattle Genetics, Inc.	1	Solid	CD70	PBD	VA	Yes	
SGN-LIV1A	Seattle Genetics, Inc.	1	Solid	LIV1	MMAE	VC	Yes	
SYD985, Trastuzumab vc-seco DUBA	Synthon BV	1	Solid	HER2	Duocarmycin	VC	Yes	

[a] No severe dose-limiting toxicity found, but two of seven evaluable patients had prolonged drug-related neutropenia after 9 mg/m^2 treatment.
TBD, to be determined; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; VC, valine-citrulline; VA, valine-alanine; MC, maleimidocaproyl linker; SMCC, *N*-succinimidyl 4-(*N*-maleimidomethyl)cyclohexane-1 carboxylate; SPDB, *N*-succinimidyl 4-(2-pyridyldithio)butyrate; SPP, *N*-succinimidyl 4-(2-pyridyldithio)pentanoate; sulfo-SPDB, *N*-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate; CL2A, maleimido-[short PEG]-Lys-PABOCO-20-O.

emtansine induced tumor regression at dose levels at or above 3 mg/kg, but more potent efficacy was observed at 15 mg/kg [13,14]. This suggests that at the clinically administered dose, ado-trastuzumab emtansine may not exert its maximal potential anti-tumor effect. Likewise, brentuximab vedotin has an MTD of 1.8 mg/kg in humans [9], while in preclinical models of Hodgkin lymphoma, the lowest dose that induced partial tumor regression was generally about 1 mg/kg dose [15], suggesting that the therapeutic index of brentuximab vedotin is fairly narrow. Other examples can be drawn from compounds in development. For example, CR011-vcMMAE (glembatumumab vedotin), an ADC that targets GPNMB, showed modest clinical activity in humans at the MTD of 1.9 mg/kg [16]. In preclinical models of melanoma CR011-vcMMAE induced complete tumor regression upon treatment with 2.5 mg/kg ADC, but the 1.25 mg/kg dose showed only modest activity [17]. Another vcMMAE conjugated antibody, MLN0264 (indusatumab vedotin) that targets guanylyl cyclase C (GCC) positive tumors, has an MTD of 1.8 mg/kg in humans [10]. Yet it has been described to show significantly better inhibition of GCC-positive xenografts at a dose of 7.5 mg/kg compared to 3.75 mg/kg dose [18].

Figure 1



Considerations for ADC design and development. Clinical efficacy of ADCs is driven by selection of the right combination of tumor antigen, targeting antibody, conjugation linker and cytotoxic payload. The expression level of ADC targets on tumor cells and healthy tissue as well as the intracellular trafficking of the antibody component are crucial parameters for selection of the most optimal linker-drug combination [65•,66,67].

In summary, these ADCs are highly active in preclinical tumor models but their therapeutic window in the clinic is narrow and dosing regimens seem hampered by dose-limiting toxicities that could not always be predicted based on data from preclinical models. This lack of predictability is especially illustrated by the fact that non-cleavable auristatin and maytansine conjugates are virtually devoid of toxicity in preclinical models at doses equivalent to the MTD for cleavable auristatin and maytansine conjugates. Yet in the clinic they induce toxicity at doses that are the same or even lower as compared to their cleavable-linked counterparts [8,13,19]. In addition several other factors make it difficult to extrapolate preclinical data to the clinic, such as differences in proliferation rates, tumor burden, multi-drug-resistance pumps and target-mediated clearance.

For most ADCs currently in clinical development, dose-limiting toxicities appear to be unrelated to the targeted antigen. For example reversible ocular toxicity specific to the cornea has been reported as the dose-limiting toxicity (DLT) for disulfide-linked DM4-conjugated antibodies targeting antigens as diverse as CD19 [7], CanAg [20], folate receptor alpha [21] and mesothelin [22], none of which are thought to have significant expression in the eye. Similar toxicity has been reported for all ADCs conjugated with MMAF via an uncleavable linker [7,23]. By contrast, no ocular toxicity has been described for a MUC16 ADC conjugated with vcMMAE, despite the fact that MUC16 expression has been described in human ocular surface epithelia [24]. In fact, most, if not all, ADCs made with vcMMAE have a similar toxicity profile, with acute neutropenia and neuropathy (upon repeated dosing) being the dose-limiting adverse events, irrespective of the target antigen, CD30 [9], PSMA [25], gpNMB [16], NaPi2b [26], MUC16 [27], GCC [10], CD22 [28] and CD79b [29]. The fact that normal tissue expression often does not drive ADC toxicity is further illustrated by clinical experience with ado-trastuzumab emtansine. HER2 expression has been described in various healthy organs such as heart, skin and epithelial cells of the gastrointestinal tract [30]. Trastuzumab, the unconjugated antibody counterpart of ado-trastuzumab emtansine, has been reported to induce cardiotoxicity in combination with chemotherapy [31], which is thought to be related to HER2 expression in the heart. By contrast, the DLT of ado-trastuzumab emtansine is reversible thrombocytopenia, thought to be an off-target toxicity, with no clinically significant toxicity reported in heart, skin or epithelial tissue [6].

However, for some ADCs, certain toxicities observed in clinical trials appear to be on-target effects. For example, in the case of glembatumumab vedotin, development of skin rash was one of the observed dose-limiting toxicities [16], which is probably due to membrane expression of gpNMB in epithelial cells of the skin [32]. Previously, development of an ADC directed against CD44v6 (bivatuzumab mertansine) was discontinued due to severe skin toxicity [33], which was also linked to high CD44v6 expression in the skin.

In general, antigens that are internalized well, with low expression on normal tissue and high expression on tumors are preferred for an ADC approach. However, the results of clinical trials indicate that it may be difficult to predict the toxicity profile based on target expression in healthy tissue. Therefore selection of antigens that are not particularly tumor specific, but highly overexpressed in tumors may, in certain circumstances, increase the efficacy of tubulin based ADCs without changing the MTD.

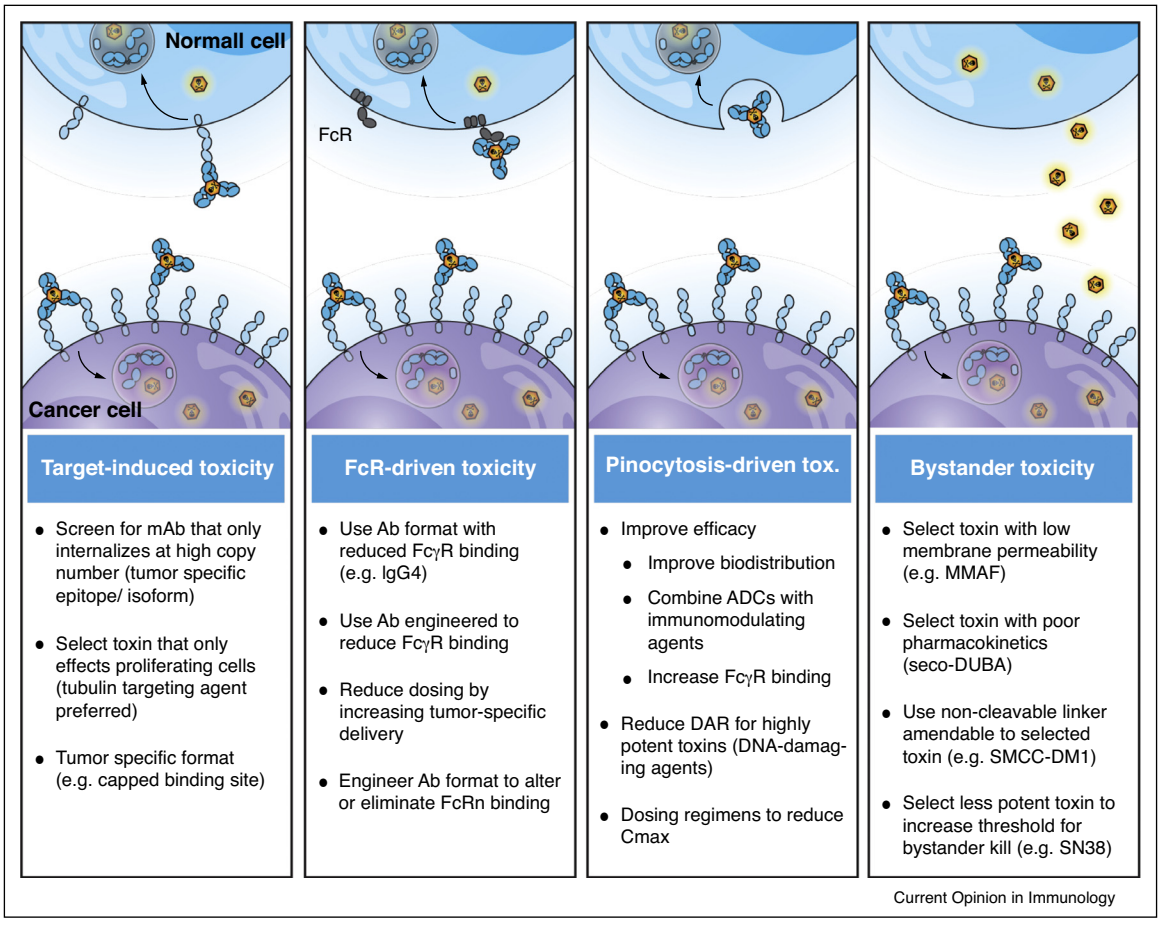
ADCs and the immune system

The mechanism behind the off-target toxicity of ADCs is poorly understood. Neutropenia and thrombocytopenia could be explained by cytotoxicity of the free payload after processing of the linker-drug by the targeted cells or in the tumor microenvironment [34]. Alternatively, uptake and processing of ADCs by Fcγ-receptor bearing cells has been proposed as a potential mechanism of toxicity (Figure 2). For example, FcγRIIa binding has been proposed to be involved in the development of thrombocytopenia induced by ado-trastuzumab emtansine. Megakaryocytes showed uptake of trastuzumab and ado-trastuzumab emtansine which could be blocked with an FcγRIIa blocking antibody. The uptake of ado-trastuzumab emtansine as well as an isotype control ADC by megakaryocytes resulted in cytotoxicity, which was not observed with unconjugated trastuzumab [35]. However, these experiments were not done in the presence of non-immune human IgG at levels comparable to those found in human blood, so it is also possible that non-specific mechanisms such as pinocytosis may contribute to uptake of ADC by antigen-negative hematological cells *in vivo* at the relatively high initial concentrations of ADC in blood plasma after administration (~0.1 mg/mL).

Whereas, on the one hand interactions with Fcγ-receptors have been implicated in toxicity of ADCs, on the other hand at least one ADC with enhanced Fc-receptor binding has entered clinical development. J6M0-mcMMAF (GSK2857916), an ADC targeting the B-cell maturation antigen (BCMA) that is selectively expressed on multiple myeloma (MM) cells, was able to eliminate MM tumors in subcutaneous and disseminated MM models. The investigators used a defucosylated antibody with enhanced affinity for FcγRIIIa expressing immune cells. J6M0-mcMMAF induced antibody-dependent cell-mediated cytotoxicity (ADCC) and macrophage-mediated phagocytosis *in vitro* and enhanced macrophage infiltration in bone marrow tissues from SCID mice bearing MM1Sluc tumors [36•].

Just as the role of IgG–FcγR interactions to toxicity is unknown, it is unclear to what extent FcγR-mediated

Figure 2



Overview of potential mechanism of toxicity induced by ADCs and strategies to minimize these toxic effects.

effector functions contribute to the clinical efficacy of ADCs. Generally, antibody-mediated effector functions were similar between the naked antibody and the corresponding ADC. Considering the two approved ADCs, the capacity of trastuzumab to induce ADCC was not affected through conjugation with DM1 [37], while brentuximab has been described to induce antibody-dependent cellular phagocytosis *in vivo*, which is believed to contribute to the potent anti-tumor efficacy observed for brentuximab vedotin [38]. Although in the latter case, the naked anti-CD30 antibody had no clinical activity [39], it may be that Fc-receptor-mediated anti-tumor activity compliments payload delivery by the ADC, for increased clinical benefit.

More recently, ADCs based on auristatins have been suggested to stimulate a tumor-specific adaptive immune response [40••]. Using fully immunocompetent mice with syngeneic RMAThy1.1 tumors, it was demonstrated that MMAE-coupled ADCs can induce dendritic cell (DC) homing to tumor draining lymph nodes. Analysis of PBMCs from Hodgkin lymphoma patients obtained before and after treatment with brentuximab vedotin showed activation of adaptive immunity as indicated by a significant decrease in the number of T-regulatory cells and increased activation of peripheral DCs and B-cells. These effects were not dependent on cytotoxicity towards the tumor cells, indicating a direct effect on DCs. Furthermore it was demonstrated that combined treatment of dolastatins with immune modulating antibodies targeting CTLA-4 and PD-1 resulted in slower outgrowth of MC38 tumors and altered ratio between regulatory and effector T-cells. These observations were also extended to maytansinoids and ado-trastuzumab emtansine [41•]. The ability of chemotherapeutic agents to stimulate immunological cell death has been widely appreciated [42]. However, the potential clinical benefit of this effect may be limited during classical chemotherapy treatment regimens, that are associated with major immunosuppressive side effects [43]. The enhanced tumor-specificity of ADCs, however, may allow for reduced immunosuppressive side effects while increasing anti-tumor immunity.

Towards more potent payloads

The clinical success of maytansinoid-based and auristatin-based ADCs has sparked increased research into evaluation of even more potent cytotoxic compounds having different cell-killing mechanisms for utilization as ADC payloads. Most such research is with DNA-damaging agents such as pyrrolobenzodiazepine (PBD) dimers [44], calicheamicins, duocarmycins [45•] and indolinobenzodiazepine dimers [46]. PBD dimers have shown promising cytotoxicity and displayed anti-tumor activity at ~10 fold lower concentration as compared to auristatins and maytansinoids. PBD dimers block cancer cell division by binding in the minor groove of DNA and crosslinking opposing strands of DNA without distorting the DNA helix, thus potentially avoiding DNA-repair mechanisms and emergent drug resistance [47]. Recently, several ADCs conjugated with PBD dimers have entered clinical development. SGN-CD33A, a humanized anti-CD33 antibody conjugated to a PBD dimer via a protease cleavable valine-alanine dipeptide linker is being tested in acute myeloid leukemia [44]. SGN-CD33A showed impressive anti-tumor activity in xenograft models at doses as low as 0.1 mg/kg of ADC. This activity was dependent on the presence of cell surface antigen, although no correlation was observed between degree of efficacy and the levels of CD33 on the cell surface [44]. The same PBD-linker format was used to develop a CD70 ADC (SGN-CD70A), for the treatment of patients with renal cell carcinoma (RCC) and non-Hodgkin lymphoma (NHL). Here too, the ADC showed impressive anti-tumor activity in preclinical models dosed at 0.1 and 0.3 mg/kg of ADC [48]. The potential of PBD dimers to target cell populations that are drug-resistant has been demonstrated with rovalpituzumab tesirine, an anti-DLL3 antibody conjugated to a PBD dimer. In patient derived xenograft models of small cell lung cancer (SCLC) the ADC was able to eradicate DLL3-positive drug-resistant tumor-initiating cells [49]. Moreover, a phase I study in patients with relapsed and refractory SCLC demonstrated that at the MTD of 0.2 mg/kg, rovalpituzumab tesirine was able to induce partial responses in 7 out of 16 patients and stable disease in a further 8 patients [50•].

Recently, SYD985, a HER2 ADC conjugated with the cleavable linker-duocarmycin analog, vc-*seco*-DUBA, entered clinical development. The ADC was able to inhibit growth of low HER2 expressing patient derived xenografts (PDX) at a single dose of 1 mg/kg [51•]. This effect may even be underestimated because vc-*seco*-DUBA conjugated ADCs have poor PK properties in mouse plasma, due to presence of mouse-specific carboxylesterase (CES1c) which can release the payload from the ADC [51•]. In human plasma, vc-*seco*-DUBA conjugated ADCs are quite stable. However, once released from the ADC, the active compound DUBA is rapidly degraded with a half-life of approximately 1 h. Although this seems unfavorable from an efficacy point of view, the rapid degradation of DUBA may also translate to lower systemic toxicity and allow for higher dosing in clinical testing [45•].

These exciting preclinical data and emerging clinical results with ADCs containing potent DNA-targeting payloads, both PBD dimers and duocarmycin based compounds, demonstrate that these ADCs are capable of inhibiting tumor growth at relatively low doses and require only modest expression of the targeted antigen. Studies addressing the safety and establishing the MTD will determine whether these extremely potent toxins can contribute to increasing the therapeutic index of ADCs towards such targets.

Summary

The increased clinical experience with tubulin-based ADCs and emerging clinical data with ADCs containing DNA-targeting payloads, help us to better understand the target requirements needed for successful ADC design. The relative lack of immunosuppressive side effects of many ADCs, suggests that a potential component of the clinical benefit obtained with some ADCs may be the engagement of the immune system. There is still much to learn about the clinical application of ADC technologies, but the success of brentuximab vedotin and ado-trastuzumab emtansine have emboldened research into improved cancer treatments utilizing ADCs that has the prospect for improved outcomes for many cancer patients.

Conflict of interest statement

John M Lambert is an employee of ImmunoGen, Inc., the developer of the maytansinoid ADC platform utilized in ado-trastuzumab emtansine and in other ADCs in clinical development, and an ADC platform based on indolinobenzodiazepines. Bart ECG de Goeij is an employee of Genmab, the developer of HuMax-TF-ADC.

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- • of special interest
- •• of outstanding interest

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