Model-Informed Therapeutic Dose Optimization Strategies for Antibody–Drug Conjugates in Oncology: What Can We Learn From US Food and Drug Administration–Approved Antibody–Drug Conjugates?

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Antibody–drug conjugates (ADCs) combine the specificity of an antibody with the cytotoxicity of a chemical agent. They represent a rapidly evolving area of oncology drug development and hold significant promise. There are currently nine ADCs on the market, more than half of which gained US Food and Drug Administration approval more recently, since 2019. Despite their enormous promise, the therapeutic window for these ADCs remains relatively narrow, especially when compared with other oncology drugs, such as targeted therapies or checkpoint inhibitors. In this review, we provide a detailed overview of the five dosing regimen optimization strategies that have been leveraged to broaden the therapeutic window by mitigating the safety risks while maintaining efficacy. These include body weight cap dosing; treatment duration capping; dose schedule (e.g., dosing frequency and dose fractionation); response-guided dosing recommendations; and randomized dose-finding. We then discuss how the lessons learned from these studies can inform ADC development going forward. Informed application of these dosing strategies should allow researchers to maximize the safety and efficacy for next-generation ADCs.

Traditional chemotherapeutic agents generally have a relatively narrow therapeutic window due to their off-target toxicity (**Figure 1**). Antibody–drug conjugates (ADCs) were initially conceptualized as a "magic bullet" for cancer treatment that would allow for selective killing of malignant cells.[1] An ADC typically consists of three components: a monoclonal antibody (mAb) that determines which cell type(s) are targeted, a cytotoxic drug that determines the mechanism of action by which cells are killed, and a chemical linker that attaches these two components together and determines how the drug is released. The mAb component of the ADC specifically is selected to target cell surface antigens overexpressed in tumor cells. Once bound, the ADC is internalized by the target tumor cell and undergoes lysosomal degradation, which releases the cytotoxic payload. This tumor-targeted delivery is expected to improve specificity and precision of the cytotoxic drug while minimizing cell killing in normal tissue and thus improving clinical safety.[2]

ADCs display unique pharmacokinetics (PK) due to their complex molecular structures, which combine the molecular characteristics of small-molecule drugs and large molecule biotherapeutics. In order to characterize an ADC's PK properties, it is generally necessary to measure multiple analytes, including conjugate (measured as either conjugated antibody or conjugated drug), total antibody (sum of conjugated, partially deconjugated, and fully deconjugated antibody), and the unconjugated drug.[3] The biodistribution of an ADC is mostly confined to the plasma, interstitial fluid, and lymphatic system.[4] ADC systemic clearance (CL) is expected to occur through proteolytic degradation and deconjugation. ADC catabolism and deconjugation *in vivo* also convert high drug–antibody ratio (DAR) species to low DAR species, leading to a dynamic change in the concentration and relative fractions of individual DAR species and a gradual decrease in average DAR over time.[5] Compared with small molecules, ADCs typically have a long residence time in systemic circulation due to neonatal Fc receptor (FcRn) recycling, allowing for less frequent dosing.[6]

Up to today, there are nine approved ADCs: enfortumab vedotin, fam-trastuzumab deruxtecan, sacituzumab govitecan, and trastuzumab emtansine that target solid tumors, while brentuximab vedotin, belantamab mafodotin, gemtuzumab ozogamicin, inotuzumab ozogamicin, and polatuzumab vedotin that target hematological cancers (**Table 1**). Prior to 2019, only one ADC, trastuzumab emtansine, was indicated for solid tumors. In 2019 and 2020, five of the ADCs were approved for solid tumor indications. In addition to tumor type, the ADCs in **Table 1** are distinguished by their immunoglobulin (IgG) isotype (IgG1 or IgG4), linker type (including cleavable and noncleavable), and cytotoxic payload (calicheamicin, mertansine (DM1), monomethyl auristatin E (MMAE), monomethyl auristatin F

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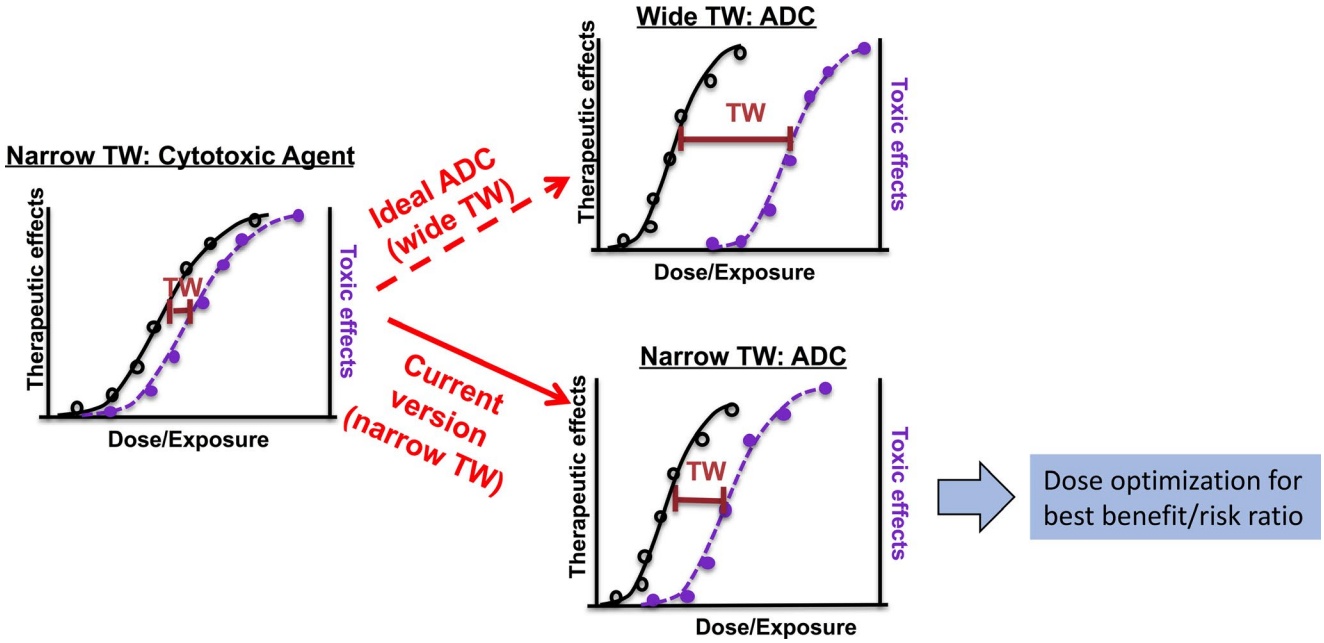

Figure 1 Key challenge of ADC development: a relatively narrow therapeutic window. ADC, antibody–drug conjugate; TW, therapeutic window.

(MMAF), protein DXd, and irinotecan metabolite SN-38), as well as the average and range DAR. The dosing schedule, key PK characteristics, and key information supporting dosing strategy for all nine US Food and Drug Administration (FDA)–approved ADCs are shown in **Table 2**. All ADCs are administered as a short intravenous (IV) infusion every 1 to 4 weeks. The dosage for each is determined by either the patient's body weight (BW, mg/kg) or body surface area (BSA, mg/m^2). Two of the nine ADCs, brentuximab vedotin and enfortumab vedotin, used BW-based dose-capping at a threshold BW (100 kg). No ADC is administered using a fixed dose.

ADCs were initially expected to have a wide therapeutic window based on the ADC design concept. Although their therapeutic window is indeed wider than that of traditional chemotherapeutic agents and they have made highly toxic payloads druggable, ADCs still have a relatively narrow therapeutic window compared with most mAbs (**Figure 1**). Toxicities such as peripheral neuropathy and cytopenia may limit the number of dosing cycles that patients can tolerate, resulting in dose delays, dose reductions, or study discontinuations. Widening the therapeutic window remains one of the most important challenges in ADC development.

Understanding the key drivers of ADC efficacy and safety is important to further improve ADC design to achieve a better therapeutic window. As shown in **Figure 2**,[7] the following mechanisms hypothetically contribute to ADC efficacy and safety and thus affect the therapeutic windows. ADC efficacy is hypothetically driven by target-dependent uptake; catabolism of an ADC results in releasing cytotoxic payload inside the tumor cell, which induces tumor cell killing. In addition, the on-target bystander effect may also occur when the cytotoxic payload is cell-permeable, diffusing through the tumor cell and killing neighboring tumor cells. The unwanted toxicity of ADCs may occur through several different mechanisms, namely nonspecific uptake of ADC by normal tissues, on-target and off-tumor toxicity due to target expression in vital normal tissues, and the associated bystander effect for the types of payloads that are cell-permeable. In addition, extracellular deconjugation and release of payload, which is determined by linker stability, may also contribute to the off-target toxicity.

Understanding the above key drivers of ADC efficacy and safety is necessary for further improving ADC design and achieving a better therapeutic window. Numerous reviews are available that have covered this topic in significant depth. Briefly, the identification of tumor-specific targets that enable efficient ADC internalization in tumor cells while having minimal expression in normal tissue is important. Linkers should be relatively stable while in systemic circulation but release the payload efficiently once the ADC is internalized into the tumor cells. ADC design using advanced technology (e.g., site-specific conjugation or novel payloads) plays a crucial role in expanding the therapeutic window of ADCs. Besides these ADC design considerations, the dose and dosing frequency optimization of ADCs during the clinical development is also critical to further optimize their therapeutic windows. We focus this review on these latter considerations.

This review evaluates nine approved ADCs and describes the five dosing regimen optimization strategies that have been leveraged to overcome narrow therapeutic windows and improve clinical outcomes for these therapies (**Figure 3**). These include: BW cap dosing; treatment duration capping; dose schedule (e.g., dose fractionation); response-guided dosing recommendations; and randomized dose-finding. We then discuss how these strategies can be applied to the development of next-generation ADCs through maximizing the efficacy benefit while minimizing the safety liability.

Table 1 Currently FDA-approved ADCs and structural properties

Generic name	Approval year	Tumor type	Indication	Antibody	Linker	Payload	DAR	Reference
Brentuximab vedotin	2011	Hematologic malignancies	cHL	Anti-CD30 IgG1	Protease-cleavable dipeptide	MMAE	4 (0, 8)	12
Trastuzumab emtansine	2013	Solid Tumor	HER2 BC	Anti-HER2 IgG1	Non-cleavable thioether	DM1	3.5 (0, 8)	59
Gemtuzumab ozogamicin	2017	Hematologic malignancies	AML	Anti-CD33 IgG4	Acid-labile: AcBut	Calicheamicin	2-3 (0, 6)	60
Inotuzumab ozogamicin	2017	Hematologic malignancies	ALL	Anti-CD22 IgG4	Acid-labile: AcBut	Calicheamicin	6 (2, 8)	61
Polatuzumab vedotin	2019	Hematologic malignancies	DLBCL	Anti-CD79b IgG1	Protease-cleavable dipeptide	MMAE	3.5 (0, 8)	62
Enfortumab vedotin	2019	Solid Tumor	Urothelial cancer	Anti-Nectin-4 IgG1	Protease-cleavable dipeptide	MMAE	4 (0, 8)	16
Fam-trastuzumab deruxtecan	2019	Solid Tumor	HER2 BC	Anti-HER2 IgG1	tetrapeptide-based cleavable linker	DXd	7-8	63
Sacituzumab govitecan	2020	Solid Tumor	TNBC	Anti-Trop-2 IgG1	hydrolysable linker (CL2A)	SN-38	7-8	64
Belantamab mafodotin	2020	Hematologic malignancies	MM	Anti-BCMA IgG1	Non-cleavable MC linker	MMAF	4	65

Abbreviations: ADC, Antibody–drug conjugate; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BCMA, B-cell maturation antigen; cHL, classical Hodgkin lymphoma; DAR, drug antibody ratio; DLBCL, diffuse large B-cell lymphoma; DM1, mertansine; DXd, an exatecan derivative; FDA, US Food and Drug Administration; HER2 BC, HER2-positive breast cancer; IgG, immunoglobulin G; MM, multiple myeloma; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; SN-38, irinotecan metabolite; TNBC, triple-negative breast cancer.

ADC Dosing Strategies

BW-based dose-capping

Tailoring ADC dosage to a patient's BW is a widely accepted method for achieving dose consistency while minimizing inter-individual variability and toxicity. It is suggested to consider the value of BW-based dosing (mg/kg) when the power exponents of BW effect on time-independent clearance and central volume of distribution is around 0.5.[8] In general, when the exponent is < 0.5, fixed dosing results in less PK variability than BW-based dosing; when the exponent is > 0.5, BW-based dosing results in less variability than fixed dosing. BW-based dosing may also lead to higher than average exposure in heavier patients. It is worth noting that BW and BSA were highly correlated; of these two covariates, BW is usually preferred to be included in the population PK model as it is the simpler measure to obtain. In fact, among the nine approved ADCs, seven of them utilized a BW-based dosing regimen with the two calicheamicin-containing ADCs using BSA-based dosing. However, no apparent evidence suggests that the adoption of BSA-based dosing was payload-dependent. A BSA-based dose capping strategy was not implemented in any of the nine approved ADCs; hence, it is beyond the scope of this review.

Underlying conditions such as diabetes and obesity in patients with cancer may contribute to the development of adverse events. The combination of anticancer agents and corticosteroids that are commonly used during cancer treatment may put diabetic patients at risk for hyperglycemia. Dose adjustment may need to be considered for mitigation risk of elevated blood glucose.[9] For obese patients, the relative percentage of lean and adipose tissue is different than that of normal-weight patients, and BW-based dosing may overcompensate for obese patients.[10] Dose-capping at a threshold BW (100 kg) for both brentuximab vedotin and enfortumab vedotin, two of the marketed vc-MMAE ADCs, reduced interindividual PK variability and the potential risk of adverse events (AEs). We discuss the BW dose-capping strategy for brentuximab vedotin and enfortumab vedotin in detail below.

Brentuximab vedotin is a CD30-directed ADC, composed of a monoclonal human/murine chimeric antibody conjugated to the microtubule-disrupting agent, MMAE, via a protease-cleavable linker.[11] Brentuximab vedotin is indicated for treatment of classical Hodgkin's lymphoma, systemic anaplastic large cell lymphoma, peripheral T-cell lymphomas, primary cutaneous anaplastic large cell lymphomas, and mycosis fungoides. Brentuximab vedotin is recommended to be administered as a monotherapy via IV infusion over 30 minutes at 1.8 mg/kg up to a maximum of 180 mg every 3 weeks (Q3W).[12] For previously untreated patients with stage III or IV classical Hodgkin's lymphoma, it is also administered in combination with chemotherapy at 1.2 mg/kg up to a maximum of 120 mg every 2 weeks (Q2W) for a maximum of 12 doses.[12] Population PK (popPK) modeling has shown that the administration of 1.2 mg/kg IV Q2W or 1.8 mg/kg IV Q3W should result in similar exposures as assessed by area under the concentration-time curve (AUC). A linear three-compartment model with zero-order input and first-order elimination describes brentuximab vedotin's clinical PK. The covariate analyses of brentuximab vedotin clinical PK indicated that BSA is a significant covariate affecting CL and volume. The

Table 2 Currently FDA-approved ADCs' dosing schedules and key information supporting dosing strategy

ADC	Dosing schedule	Key PK characteristics	Key information supporting dosing strategy	Ref
Gemtuzumab ozogamicin	Adults: Newly diagnosed, *de novo* AML (combination regimen): Induction: 3 mg/m^2 on Days 1, 4, and 7 in combination with daunorubicin and cytarabine. Consolidation: 3 mg/m^2 on Day 1 in combination with daunorubicin and cytarabine. Adults: Newly diagnosed AML (single-agent regimen): Induction: 6 mg/m^2 on Day 1 and 3 mg/m^2 on Day 8. Continuation: For patients without evidence of disease progression following induction, up to eight continuation courses of Mylotarg 2 mg/m^2 on Day 1 every 4 weeks.	Half-life: 3.75 days after second dose Accumulation: ~ twofold higher AUC for doses 2 weeks apart. Evidence for target-mediated drug disposition.	Key toxicities impacting dose tolerability: TCP, VOD, septic shock. Positive correlation between C_{max} and VOD	24,60
Inotuzumab ozogamicin	Dosing regimens for Cycle 1 and subsequent cycles, depending on the response to treatment, are shown below. See full prescribing information for dosing details.	Half-life: 12.3 days Accumulation: 5.9-fold higher AUC for Cycle 4 vs. Cycle 1 in patients with ALL. Target-mediated drug disposition dependent on disease (e.g., NHL vs. ALL).	Key toxicities impacting dose tolerability: Infection, TCP, hyperbilirubinemia, transaminases increased, hemorrhage, neutropenia, febrile neutropenia. VOD in 14% of patients Liver function abnormalities, occasional VOD after allogeneic SCT, and transient febrile and hypotensive episodes were less frequent for fractionated vs. higher single dose, suggesting possible C_{max}-driven effects.	40,61,66
Enfortumab vedotin	The recommended dose of Padcev is 1.25 mg/kg (up to a maximum dose of 125 mg) given as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity.	Half-life: 3.4 days Minimal accumulation	Key toxicities impacting dose tolerability: peripheral neuropathy, rash, and fatigue. Exposure–response analyses inconclusive.	16,33
Sacituzumab govitecan	The recommended dose of Trodelvy is 10 mg/kg given as intravenous infusion once weekly on Days 1 and 8 of continuous 21-day treatment cycles until disease progression or unacceptable toxicity.	Half Life: 0.67 days No accumulation	Key toxicities impacting dose tolerability: Anaphylaxis, anorexia/fatigue, headache, neutropenia/febrile neutropenia. Possible relationship between C_{max} and neutropenia (data limited). Exposure-efficacy inconclusive	33,64

	Day 1	Day 8	Day 15
Dosing regimen for Cycle 1			
All patients:			
Dose	0.8 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	21 days*		
Dosing regimen for subsequent cycles depending on response to treatment			
Patients who have achieved a CR or CRi:			
Dose	0.5 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	28 days		
Patients who have not achieved a CR or CRi:			
Dose	0.8 mg/m^2	0.5 mg/m^2	0.5 mg/m^2
Cycle length	28 days		

*For patients who achieve a CR or a CRi, and/or to allow for recovery from toxicity, the cycle length may be extended up to 28 days (i.e., 7-day treatment-free interval starting on Day 21).

(Continued)

Table 2 (Continued)

ADC	Dosing schedule	Key PK characteristics	Key information supporting dosing strategy	Ref
Polatuzumab vedotin	The recommended dose of Polivy is 1.8 mg/kg as an intravenous infusion over 90 minutes every 21 days for 6 cycles in combination with bendamustine and a rituximab product. Subsequent infusions may be administered over 30 minutes if the previous infusion is tolerated.	Half-life of conjugate (acMMAE): ~ 12 days (95% CI: 8.1–19.5 day) Moderate accumulation (30% higher in Cycle 3 than Cycle 1 by Q3W regimen)	Key toxicities impacting dose tolerability: peripheral neuropathy and hematological AEs (e.g., neutropenia, anemia) Grade 2+ PN increase with conjugate (acMMAE) dose, AUC, and treatment duration	21,67
Brentuximab vedotin	Single-agent regimen: The recommended dose of Adcetris as monotherapy is 1.8 mg/kg up to a maximum of 180 mg every 3 weeks. Combination regimen: The recommended dose of Adcetris in combination with chemotherapy for previously untreated stage III or IV cHL is 1.2 mg/kg up to a maximum of 120 mg every 2 weeks for a maximum of 12 doses. The recommended dose of Adcetris in combination with chemotherapy for previously untreated PTCL is 1.8 mg/kg up to a maximum of 180 mg every 3 weeks for 6–8 doses.	ADC half-life: ~ 4–6 days. 1.8 mg/kg Q3W: minimal to no accumulation of ADC was observed. 1.2 mg/kg Q2W: 1.27-fold accumulation (14-day AUC) was observed.	Key toxicities impacting dose tolerability: Peripheral neuropathy, neutropenia (FN) grade 2+ PN, and grade 4+ FN increase with conjugate AUC and treatment duration	12,22,68
Trastuzumab deruxtecan-	The recommended dosage of Enhertu is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.	ADC half-life ~ 5.7 days. Accumulation was ~ 35% at steady state (Cycle 3).	Statistically significant relationship between (fam-) trastuzumab deruxtecan exposures (C_{trough}) vs. overall response rates (ORRs) and best tumor response (BTR), with a trend toward higher progression-free survival (PFS) at higher exposures were observed. Statistically significant relationships were observed for (fam-) trastuzumab deruxtecan and the payload, DXd, exposures (C_{max}/ AUC) and key AEs (i.e., any grade ILD, any grade or grade ≥3 anemia, any grade or grade ≥3 neutrophils/ platelet count decreases).	63,69

(Continued)

Table 2 (Continued)

ADC	Dosing schedule	Key PK characteristics	Key information supporting dosing strategy	Ref
Belantamab mafodotin	The recommended dosage of Blenrep is 2.5 mg/kg of actual body weight as an intravenous infusion over ~ 30 minutes once every 3 weeks until disease progression or unacceptable toxicity.	The terminal phase half-life of belantamab mafodotin-blmf was 12 days after the first dose and 14 days at steady state. Accumulation was ~ 70% with a Q3W dosing regimen	The probability of treatment response (PoR) and PFS were not related to drug exposure, while the time to response (TTR) was inversely related to the trough concentration (C_{trough}) of the ADC. Higher payload (cys-mcMMAF) exposures (C_{max}) were associated with increased probability of ≥3 TCP. Higher ADC C_{trough} was associated with the increased probability of developing grade ≥2 or ≥3 ocular exam finding (OEF) and inversely correlated to time to onset of OEF.	65,70
Trastuzumab emtansine	The recommended dose of Kadcyla is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity, or a total of 14 cycles.	The elimination half-life of trastuzumab emtansine was 4 days. No accumulation was observed after repeated dosing of intravenous infusion every 3 weeks	Key toxicities impacting dose tolerability: TCP and hepatotoxicity No significant exposure–safety relationship was observed. Exposure–efficacy relationship is likely confounded.	71–73

acMMAE, antibody-conjugated MMAE; ADC, antibody–drug conjugate; AEs, adverse events; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; CR, complete remission, CRi, complete remission with incomplete hematologic recovery; C_{trough}, minimum circulating concentration; cys-mcMMAF, cysteine-maleimidocaproyl MMAF; DXd, an exatecan derivative; FDA, US Food and Drug Administration; FN, febrile neutropenia; ILD, interstitial lung disease; mcMMAF, maleimidocaproyl MMAF; NHL, non-Hodgkin's lymphoma; PK, pharmacokinetics; PN, peripheral neuropathy; PTCL, peripheral T-cell lymphoma; SCT, stem cell transplant; TCP, thrombocytopenia; VOD, veno-occlusive disease.

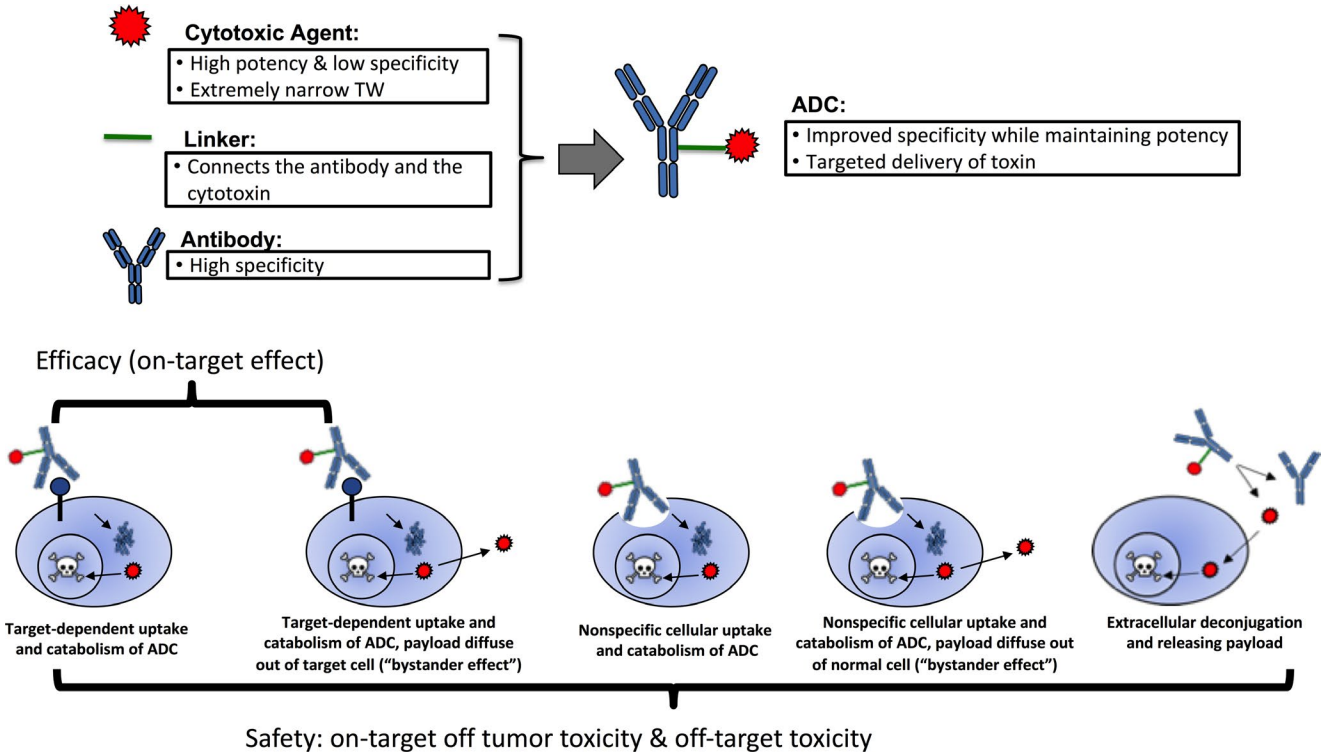

Figure 2 Key design considerations for maximum benefit/risk ratio. ADC, antibody–drug conjugate; TW, therapeutic window.

effect of the model estimate of the covariate effects of BSA on the CL (1.1), central volume of distribution (0.893), and peripheral volume of distribution 2 (1.47) of ADC was simulated. The analysis suggested an increasing AUC with increasing body size (BSA or BW) but with a substantial overlap in predicted exposures across the BSA range.[13,14]

In order to avoid overdose in heavier patients, patients were dosed at 1.2 mg/kg for patients less than 100 kg and a fixed dose, 120 mg, for patients weighing more than 100 kg. With a capped dose of 120 mg in patients with BW higher than 100 kg ($N = 51$), the simulated AUC values for brentuximab vedotin showed that AUC for both brentuximab vedotin and unconjugated MMAE increased with increasing body size up to 100 kg and then decreased as expected for the lower mg/kg dose in higher BW patients.[13] Based on the simulation without BW capping, a patient with a BW of 105 kg would be expected to have an AUC that is 121% that of a patient with a median BW of 71 kg.[14] In general, BW capping may improve the ADC's safety profile. BW dose-capping reduced the overall interindividual variability for exposure. The incidence of diarrhea and fatigue increased in patients weighing more than 100 kg without a BW cap. However, the number of patients weighing more than 100 kg was low, making it more difficult to interpret the correlation between PK, BW, and treatment efficacy.[15] Based on exposure–response analyses, exposures with BW capping achieved with 1.2 mg/kg brentuximab vedotin Q2W resulted in similar efficacy across all quartiles of the ADC AUC/time. There is no evidence to suggest that increasing the dose of brentuximab vedotin would lead to any further improvement in efficacy.[13] Based on the simulated exposure, a maximum dose of 120 mg Q2W or 180 mg Q3W for a BW of 100 kg is appropriate in the overall adult population.[14]

A similar BW-based dose-capping dose strategy was used for enfortumab vedotin, an ADC indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer. Enfortumab vedotin is recommended at 1.25 mg/kg with a maximum dose of 125 mg.[16] An initial phase I study suggested that single-agent enfortumab vedotin was generally well tolerated and provided clinically meaningful and durable responses in patients with metastatic urothelial carcinoma.[17] In addition, popPK and modeling and simulations analyses were used to support weight-based dosing for enfortumab vedotin. The model identified BW as a significant covariate influence on enfortumab vedotin. The model estimate of the covariate effects of weight on the CL was 0.656, and the central volume of distribution was 0.592.[18] Initially, the BW cap was set at 120 kg, leading to a permitted maximum dosage of 150 mg. However, four of the five total drug-related severe adverse events occurred in subjects with BW >100 kg ($N = 22$). Therefore, clinical protocols were subsequently amended, including the BW cap being reduced from 120 kg to 100 kg. The investigators also sought to understand whether a BW cap lower than 100 kg would be appropriate. Simulated Cycle 1 AUC, maximum concentration (C_{max}), and minimum circulating concentration (C_{trough}) for enfortumab vedotin and unconjugated MMAE were compared for BW caps (dosages) > 100 kg (125 mg) and > 85 kg (106 mg). The lower weight cutoff of 85 kg produced more variability and less consistency of exposures, particularly for subjects > 100 kg, compared with a higher weight cutoff of 100 kg, suggesting that the higher BW dose cap is more appropriate. Thus the final recommendation for dose individualization on the basis of BW was to put the threshold at a maximum dose of 125 mg.[18]

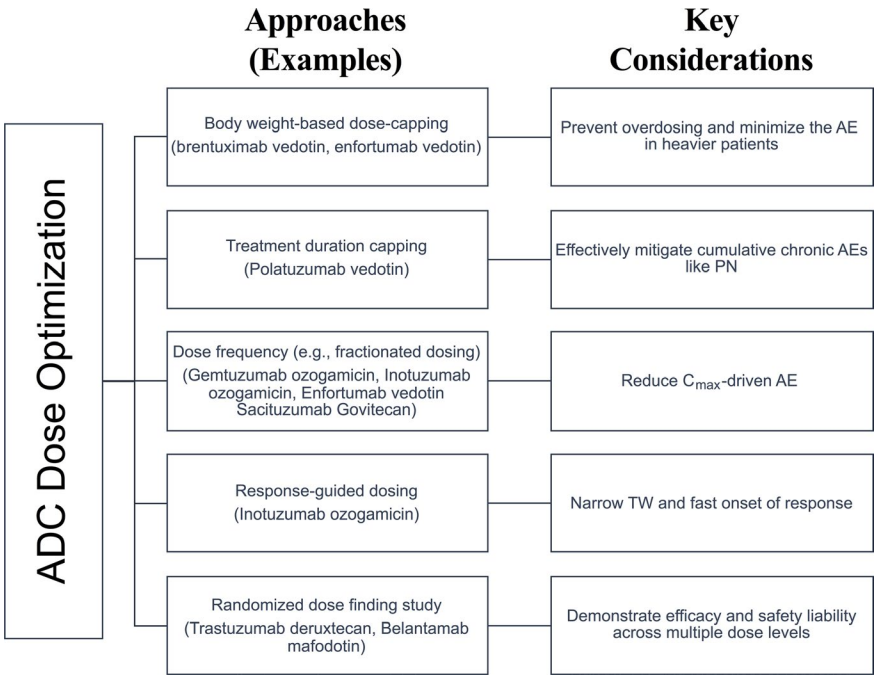

Figure 3 ADC dose optimization overview and key considerations. *Note:* trastuzumab emtansine has not been categorized into a specific dosing strategy, though the different dosing frequency (e.g., QW vs. Q3W) was evaluated, and exposure–response analysis showed that the 3.6 mg/kg Q3W regimen is appropriate. ADC, antibody–drug conjugate; AE, adverse event; C_{max}, maximum concentration; PN, peripheral neuropathy; TW, therapeutic window.

Treatment duration capping

Capping the treatment duration of an ADC is a dose optimization strategy for mitigating the risk of chronic AEs that emerge during repeated dosing. Peripheral neuropathy (PN) is an AE generally associated with ADCs containing a potent antimitotic agent as the payload, for example, MMAE. MMAE is a synthetic auristatin derivative that inhibits cell division and promotes apoptosis by binding to tubulin and disrupting the microtubule network.[19] PN events are generally chronic, with delayed emergence over time and progressive worsening upon repeated dosing.[19,20] Exposure–response analysis by logistic regression was first performed to understand the empirical relationship between the incidence of PN and systemic exposure of ADC-related analytes (e.g., conjugated payload and unconjugated payload). It was found that for multiple MMAE-containing ADCs, such as polatuzumab vedotin and brentuximab vedotin, the probability of grade ≥2 PN is correlated with the systemic exposure of the conjugate, measured as antibody-conjugated MMAE (acMMAE) or conjugated antibody, but not with the systemic exposures of unconjugated MMAE.[3,14,21,22] Hypothetically, the circulating acMMAE is taken up by body tissues in a specific or nonspecific way, is degraded within lysosomes, and releases unconjugated MMAE, which may be subsequently distributed to nearby neurons to induce PN. Thus, the circulating acMMAE may play an important role in the delivery of MMAE to nerve tissues, leading to the observed correlation with the incidence of PN.

Since PN is a delayed AE driven by conjugate exposure and duration of treatment, and the conjugate (acMMAE) exposures are driven by ADC dose and schedule, the type of parametric time-to-event (TTE) model to quantify the relationship between the conjugate PK and time to the onset of grade ≥2 PN was performed to allow for an informed selection of the ADC dose and regimen that mitigated the occurrence risk of a PN AE.[19,20] For polatuzumab vedotin, a TTE model was established to describe the hazard rate of the first occurrence of grade ≥2 PN events at each timepoint as a function of acMMAE PK, with a delayed effect and time-dependent increase by Weibull distribution. The model predicted that PN incidence of grade ≥2 by treatment of six and eight cycles is 19% and 31%, respectively, at 1.8 mg/kg Q3W, and 27% and 41%, respectively, at 2.4 mg/kg Q3W. The risk ratio of 2.4 mg/kg to 1.8 mg/kg for six and eight cycles is ~ 1.4:1 and 1.3:1, respectively, with 90% confidence interval excluding 1. In general, these incidences are comparable with treatment-induced PN rates of 30–40% observed for other antimicrotubule chemotherapeutic agents, such as liposomal vincristine.[19] These results suggested that capping the treatment duration to 6–8 cycles at 1.8 mg/kg Q3W is desirable to mitigate PN risks. Furthermore, a separate analysis leveraging eight MMAE-containing ADCs (~ 700 patients) identified that PN risk increased with conjugate exposure, treatment duration, BW, and previously reported PN. Patients with prior PN have ~ 50% higher hazard of grade ≥2 PN.

It is worth noting that a typical 100-kg patient has ~ 40% higher PN risk than a typical 75-kg patient. BW appears to be a PN risk factor independent of drug exposure, as the increased exposure in high-BW patients given per mg/kg dose was not sufficient to explain the impact of BW on the observed incidence of PN. As a result, the model simulation suggested that capping the dose for patients > 100 kg only had a marginal benefit for these patients in reducing the PN risk.[20] The increased risk associated with a high BW might be related to increased height and hence increased

length and surface area of the axonal nerve fibers being available for the ADC exposure.[23]

Taken together, these TTE analyses showed that both dose level and treatment duration can be modulated to mitigate the risk of PN induced by MMAE-containing ADCs, while BW-based dose capping did not appear to mitigate PN risk in a clinically meaningful way, based on the model simulation.[20] These analyses were used to support the label dose of 1.8 mg/kg Q3W for six cycles for polatuzumab vedotin to treat relapsed/refractory diffuse large B-cell lymphoma.[12] The dosing schedule optimization strategy presented here can be further extended to other delayed/chronic AEs for other ADCs in future development.

Dosing frequency

Leveraging PK and PD information to inform dosing frequency and treatment-free intervals are essential in maintaining efficacy and safety while simultaneously improving patient convenience. The ADC half-life does not appear to be a main driver to determine the optimal dosing frequency. Across the majority of the nine ADCs reviewed, the dosing interval was substantially longer than would be predicted based on half-life (**Table 2**). For an IV-administered drug, a less frequent higher dosing regimen is generally preferred to a more frequent lower dose from the perspective of patient convenience; less frequent dosing of Q2W or Q3W is used for five of the nine ADCs. However, it is notable that four of the approved ADCs incorporate weekly dosing in the label for some or all doses within a cycle: gemtuzumab ozogamicin, inotuzumab ozogamicin, sacituzumab govitecan, and enfortumab vedotin. This suggests that for some of the ADCs the more frequent dose schedule provides an advantage by widening the therapeutic window, despite the potential inconvenience (**Table 2**). Additionally, while not a label dose schedule, brentuximab vedotin has also been tested in patients using a weekly dose schedule, as discussed later in this section.

When a single higher dose is divided into multiple lower doses that yield the same cumulative dose per cycle (e.g., 9 mg/kg every 3 weeks divided into 3 mg/kg weekly), the fractionated dose yields a similar cumulative AUC, lower C_{max}, and a higher C_{trough} compared with the higher single dose for ADCs with linear, time invariant PK. Thus, fractionated dosing may be expected to improve the therapeutic window for C_{max}-driven toxicity and/or C_{trough}-driven efficacy. Fractionated doses may be evenly distributed within a dosing cycle. Alternatively, higher dose levels may be followed by lower dose levels if target mediated drug disposition and/or strong initial efficacy is desired, or a dosing holiday may be incorporated at the end of the cycle to allow for recovery from toxicities. Given the correlation often seen between C_{max}, AUC, and C_{trough}, data from fractionated vs. nonfractionated regimens yielding the same cumulative AUC are often required in order to correctly identify the key exposure driver, which is important for selecting the appropriate exposure metric to characterize the exposure–response relationships.

Among approved ADCs, the advantage of dose fractionation has been best established for gemtuzumab ozogamicin, an ADC consisting of a CD33-directed mAb conjugated with calicheamicin payload, which was the first approved ADC in the United States. More frequent, smaller doses over a dosing cycle rather than a single, less frequent, larger dose may provide similar efficacy outcomes but improve the tolerability of the medication. In 2000, gemtuzumab ozogamicin was granted accelerated approval as monotherapy at a dosing regimen of 9 mg/m^2 IV Q2W for two total doses for the treatment of relapsed, chemotherapy ineligible, CD33-positive acute myeloid leukemia (AML) in patients who are 60 years or older.[24] Following approval, higher incidence of fatal hepatotoxicity and veno-occlusive disease (VOD) were observed in clinical practice, compared with rates during the registrational trial, requiring the addition of a boxed warning for these toxicities to be added to the label. Subsequently, new study results indicated that a lower dose of 6 mg/m^2 in combination with daunorubicin/cytarabine in *de novo* AML patients younger than 60 years was not more efficacious than the standard of care.[24] As a result, gemtuzumab ozogamicin was withdrawn from the market in 2010.

Gemtuzumab ozogamicin was reapproved as a new biologic license application in 2017 at a lower or "fractionated" dosing regimen of 3 mg/m^2 on Days 1, 4, and 7 in combination with daunorubicin and cytarabine in *de novo* AML patients aged 50–70 years.[24] The fractionated dosing regimen was selected to administer a smaller gemtuzumab ozogamicin dose more frequently to achieve lower gemtuzumab ozogamicin C_{max} and AUC compared with the original biweekly dosing schedule (9 mg/m^2 Q2W). This was supported by PK characteristics and the known mechanism of action for gemtuzumab ozogamicin. Per popPK modeling and pharmacodynamics data, gemtuzumab ozogamicin has a short half-life of 62–90 hours. Mild drug accumulation is expected with more frequent gemtuzumab ozogamicin dosing. The target receptor saturation studies also indicated doses of 2 mg/m^2 or higher would achieve >90% saturation of CD33 receptors.[24] In addition, *in vivo* and *in vitro* studies showed rapid re-expression of CD-33 receptors after gemtuzumab ozogamicin administration, one of the rationales to support the more frequent fractionated dosing of gemtuzumab ozogamicin.[25,26] A single phase III, randomized clinical trial confirmed the fractionated dosing regimen of 3 mg/m^2 on Days 1, 4, and 7 for gemtuzumab ozogamicin in combination with chemotherapy had statistically better event-free survival (HR 0.66; 95% confidence interval: 0.49–0.89; two-sided P = 0.006) and higher overall survival in *de novo* AML patients aged 50–70 years, compared with chemotherapy alone.[27,28]

Based on historical clinical data, exposure–response, target site saturation, and benefit–risk profile of the fractionated dose in the *de novo* AML patients, the dosing regimen of 3 mg/m^2 on Days 1, 4, and 7 was extended and approved for the reapplication of gemtuzumab ozogamicin as monotherapy for the treatment of relapsed AML with a postmarket recommendation.[24] Although no PK data was collected at the fractionated dosing regimen of 3 mg/m^2 on Days 1, 4, and 7 for gemtuzumab ozogamicin, simulations using the previously developed popPK model were performed to predict mean Cycle 1 C_{max} at 2, 3, 4, and 9 mg/m^2 doses of gemtuzumab ozogamicin and were put in combination with clinical efficacy and safety data collected across all clinical trials for exposure–efficacy and exposure–safety analysis.[29] The exposure–efficacy relationship confirmed clinical trial observations that efficacy outcomes were similar for the exposure levels from the 3 mg/m^2 and 9 mg/m^2 doses

of gemtuzumab ozogamicin ($P = 0.605$, after adjustment of baseline disease). Additionally, clinical trials confirmed the fractionated 3 mg/m^2 on Days 1, 4, and 7 IV dosing regimen for gemtuzumab ozogamicin was associated with reduced VOD and early mortality compared with the 9 mg/m^2 dosing. This aligns with gemtuzumab ozogamicin demonstrating C_{max}-driven toxicities, that is VOD was recognized to be driven by C_{max} from exposure–response analyses.[24] This case of dose fractionation is an example where the optimal dosing regimen was more frequent lower doses compared with the first marketed biweekly gemtuzumab ozogamicin dosing regimen. The dose fractionation strategy optimized the benefit–risk profile for gemtuzumab ozogamicin.

Inotuzumab ozogamicin is a CD22-directed mAb, calicheamicin-containing ADC. Similar to gemtuzumab ozogamicin, inotuzumab ozogamicin also implements a fractionated dose schedule that appears to improve the therapeutic window by mitigating C_{max}-driven toxicities. In a clinical study of repeated 3-week or 4-week cycles comparing a single dose to three fractionated weekly doses per cycle yielding a similar cumulative dose, liver function abnormalities, occasional VOD after allogeneic SCT, and transient febrile and hypotensive episodes were less frequent for the fractionated dosing schedule, suggesting the dosing-related toxicities are most probably related to peak levels consistent with C_{max}-driven effects. In contrast, bone marrow response rate for inotuzumab ozogamicin treatment was associated with the total AUC, which was similar for both schedules.[30] Therefore, these data suggest that the mechanism by which fractionated inotuzumab ozogamicin dosing maximizes the therapeutic window may be largely driven by mitigating C_{max}-driven toxicities while sustaining efficacy.

For enfortumab vedotin, a nectin-4-directed, MMAE-containing ADC administered on Days 1, 8, and 15 of each 28-day cycle, the rationale for dose fractionation is less clear. Key toxicities impacting dose strategy are shown in **Table 2**. While positive correlations were seen between C_{max} and/or AUC for some safety end points, these were of limited clinical relevance (e.g., correlation of peripheral neuropathy with C_{max}) or did not have a clearly stronger correlation with C_{max} compared with AUC.[18] Therefore, unlike gemtuzumab ozogamicin and inotuzumab ozogamicin, there are no convincing data to suggest that fractionated dosing provides benefit by mitigating C_{max}-driven toxicities.

Grade 3–4 neutropenia was seen in ~ 5% of patients treated with enfortumab vedotin,[18] consistent with myelosuppression that is commonly seen for other antimitotic therapies[31] and attributed to effects on neutrophil production in the bone marrow.[32] Given the potential effect of MMAE on myeloid progenitors, incorporating a recovery period may be important to limit myelosuppressive toxicities. Therefore, it is noteworthy that enfortumab vedotin includes a 2-week recovery period between the last dose of one cycle and the first dose of the subsequent 28-day cycle.

The rationale for an optimal recovery period at the end of each cycle of enfortumab vedotin administration is not firmly established from available published data. Exposure–safety analyses did not conclusively distinguish C_{max} from AUC-driven neutropenia.[33] For all ADCs reviewed, although adverse event rates cannot be directly compared across studies, it is notable that weekly doses of 1.25 mg/kg enfortumab vedotin on Days 1, 8, and 15 of a 4-week cycle (3.75 mg/kg cumulative dose over 4 weeks), with a 2-week recovery period, yielded manageable levels of neutropenia (~5% grade 3–4 in urothelial cancer) despite a higher cumulative dose and shorter recovery time between cycles compared with other marketed MMAE-containing ADCs that are dosed as monotherapy at 1.8 mg/kg Q3W (2.4 mg/kg cumulative dose over 4 weeks), where neutropenia rates were ~ 27% grade 3-4 for polatuzumab vedotin in chronic lymphocytic leukemia / non-Hodgkin's lymphoma and from 5% to 39% for brentuximab vedotin across lymphoma subtypes.[14,16,34]

Enfortumab vedotin showed no clear evidence for improvement in efficacy for fractionated vs. nonfractionated dosing in xenograft orthotropic breast cancer and xenograft bladder cancer models.[35] Based on clinical data in patients with metastatic urothelial carcinoma, exposure–efficacy analyses did not conclusively distinguish C_{max} from AUC-driven responses.[33]

For brentuximab vedotin, an MMAE-containing ADC, which has been tested in patients using Q3W, Q2W, and weekly dose schedules,[36,37] a clinical study employing a weekly dosing schedule may play a role in the safety profiles. The weekly regimen (weekly for 3 weeks of a 4-week cycle) of brentuximab vedotin is associated with 73% of any grade PN events (dose range 0.4–1.4 mg/kg, $N = 44$). This is markedly higher than the 22% PN event incidence observed during the Q3W regimen (dose range 0.1–3.6 mg/kg, $N = 45$).[36,37] The overall antitumor responses were similar between the two regimens at the maximum tolerated dose (MTD) of each regimen (objective response: 50% of 12 patients for 1.8 mg/kg Q3W and 58% of 12 patients for 1.2 mg/kg weekly for 3 weeks of a 4-week cycle. This higher incidence of PN events in the weekly regimen is potentially due to a higher total ADC dose and/or more frequent dosing. As a result, Q3W and Q2W regimens are the approved regimen for brentuximab vedotin, while the weekly regimen was not further developed.[12] The learnings from brentuximab vedotin contributed partially to the selection of polatuzumab vedotin, another MMAE-containing ADC. The Q3W over a weekly dosing schedule for clinical development of polatuzumab vedotin was tested, and Q3W is the currently approved regimen.

Sacituzumab govitecan is a trop-2 directed ADC conjugated to SN-38, a topoisomerase I inhibitor. Key toxicities impacting dose strategy are shown in **Table 2**. Exposure–response analyses showed a positive correlation between the probability of any grade neutropenia and increased C_{max} of total SN-38, but are based on a small sample size, with all patients treated at a single dose level. Although some other AEs showed positive correlations with exposure of sacituzumab govitecan analytes, these were related to AUC, not C_{max}, and subject to the same dose and sample size limitations. Overall, although the safety data are inconclusive, it is possible that fractionated dosing could reduce C_{max}-driven toxicity for neutropenia.

Given the mechanism of action, topoisomerase I payloads would be expected to affect predominantly dividing cells.[38] Similar to MMAE, sacituzumab govitecan may require a recovery period, and indeed, the recommended fractionated dosing schedule of 10 mg/kg given on Days 1 and 8 of a Q3W cycle

incorporates a 2-week recovery period between last dose of one cycle and first dose of next cycle. However, there are insufficient reported clinical data to determine if this schedule provides an optimal recovery period.

Sacituzumab govitecan showed no significant improvement in efficacy for fractionated vs. nonfractionated dosing in pancreatic and gastric xenograft tumor models,[39] suggesting that C_{trough} is not driving efficacy. This finding is notable given that sacituzumab govitecan has a relatively short half-life of 11 hours for the intact conjugate in mice, which would greatly increase the ability to detect C_{trough}-driven effects. Exposure–efficacy analyses in patients were inconclusive. Overall, as for the other ADCs incorporating more frequent dosing schedules, the value of fractionated dosing for sacituzumab govitecan seems to be best supported by data suggesting mitigation of toxicities.

Overall, based on review of publicly available data for approved ADCs, the rationale for improved therapeutic windows with more frequent lower doses is most strongly established for gemtuzumab ozogamicin and inotuzumab ozogamicin, and appears largely driven by mitigating VOD and possibly other C_{max}-driven toxicities. For enfortumab vedotin and sacituzumab govitecan, the rationale for more frequent dosing is less strongly established in the literature from either a safety or efficacy perspective. Across the majority of the nine ADCs reviewed, the dosing interval was substantially longer than would be predicted to maintain C_{trough} levels based on half-life. For all four ADCs with fractionated schedules, there were no definitive data showing higher efficacy for fractionated vs. nonfractionated dosing schedules, suggesting that maintaining trough levels above some minimum threshold may not be critical to achieving efficacy for these ADCs. Three of the four ADCs which include weekly dosing for some or all of a treatment cycle incorporate a recovery period at the end of each cycle. For drugs with myelosuppressive toxicities, including neutropenia, this strategy may allow time for bone marrow recovery. For inotuzumab ozogamicin, a 2-week recovery period does not appear to be sufficient for the ADC to be washed out of the circulation, given the relatively long half-life of ~ 12 days. Therefore, a two-week recovery period may be of limited value to recover the bone marrow and other toxicities. In contrast, enfortumab vedotin and sacituzumab govitecan have half-lives of 3.4 days and 0.67 days respectively, which are relatively short compared with the 2-week recovery period employed for these ADCs. Therefore, the recovery period for these molecules could be sufficient to enable bone marrow recovery. Overall, the ADC half-life does not appear to consistently predict optimal dosing frequency or recovery period for the ADCs reviewed. Undoubtedly, the lower weekly dose has proven beneficial for optimizing drug tolerability to C_{max}-driven or dose-related toxicities, such as VOD for gemtuzumab ozogamicin and inotuzumab ozogamicin. Overall, identification of the optimal dosing frequency benefits from clinical or nonclinical identification of the exposure metric (e.g., C_{max}, AUC, or C_{trough}) that drives efficacy and major or serious toxicities, receptor or cell turnover, and optimal recovery times from toxicities. With this information, dosing schedules that maximize the therapeutic window can be implemented to provide the best outcomes for patients.

Response-guided dosing

Adaptive dosing strategy involves adjusting the therapeutic dose based on individual patient response. Inotuzumab ozogamicin used an adaptive dosing strategy based on early efficacy signals to enable a response-guided dosing regimen to accommodate inotuzumab ozogamicin toxicity (e.g., thrombocytopenia (TCP) and VOD) and inotuzumab ozogamicin response-driven nonlinear PK with multiple doses (e.g., increased exposure in complete remission (CR) / complete remission with incomplete hematologic recovery (CRi) responders). Inotuzumab ozogamicin is initially dosed at 1.8 mg/m^2 per cycle at Cycle 1 and, for Cycle 2 onwards, either reduced to 1.6 mg/m^2 per cycle for complete remission/complete remission with incomplete hematologic recovery (CR/CRi) responders or resumed at 1.8 mg/m^2 per cycle if CR/CRi is not achieved.[40] The rationale for the 1.6 mg/m^2 dose reduction in responders is to help reduce toxicity since higher inotuzumab ozogamicin exposure was observed in CR/CRi responders, suggesting tumor burden or blast count may influence inotuzumab ozogamicin drug clearance (i.e., response-dependent PK) and be a reflection of on-target receptor binding or efficacy. In clinical trials, dose modifications are common in later cycles of treatment and the majority of patients receiving 1.8 mg/m^2 per cycle experienced AEs leading to dose delays (78%) or reductions (22%).[41]

For oncology, the therapeutic dose is typically associated with the highest tolerated or assessed dose. Clinicians observed inotuzumab ozogamicin dose-limiting AEs (grade 4 TCP, injury-related bleeding requiring plattelet transfusion) both at and below the MTD of 1.8 mg/m^2 Q4W in a phase I study in patients with B-cell non-Hodgkin's lymphoma.[41] Additionally, numerous dose delays from AEs led to early treatment discontinuation at the MTD, limiting the median number of cycles received in therapy to 2–3 cycles. Another phase I/II study in patients with acute lymphoblastic leukemia (ALL) tested three dosing regimens of 1.2 (N = 3), 1.6 (N = 12), and 1.8 mg/m^2 (N = 9) (total dose) given in three divided doses over a 28-day dosing cycle that showed promising efficacy CR/CRi rates of 67%, 75%, and 89%, with two, eight, and eight patients achieving minimal residual disease negativity, respectively.[42] No dose-limiting toxicities were observed in the 1.2 and 1.6 mg/m^2 dosing cohorts, and 1 dose-limiting toxicity in the 1.8 mg/m^2 cohort.[42] These compelling phase I results drove early dosing decisions to select 1.8 mg/m^2 given in 3 divided doses over a 28-day dosing cycle as the recommended phase II dose in patients with ALL. However, the previously established response-driven PK and high rates of treatment discontinuation at doses of 1.8 mg/m^2 in another clinical trial drove the decision to reduce the dose to 1.6 mg/m^2 in subsequent cycles for responders. A subsequent phase III pivotal trial was conducted to confirm the efficacy and safety of the 1.8 mg/m^2 (given in 3 divided doses over a 28-day dosing cycle) dosing regimen with the response-guided dosing.[43,44]

The combined phase I and III data showed a significant exposure–efficacy relationship between average concentration (C_{avg}) and efficacy outcomes (CR/CRi and minimal residual disease; P value <0.0001), but they also showed a significant exposure–safety relationship with VOD. Furthermore, the phase III study results showed high overall rates of post–hematopoietic stem cell transplantation, nonrelapse mortality, and VOD (22%

inotuzumab ozogamicin treatment vs. 3% control).[43,44] These toxicity findings were similar to those observed for the previously approved calicheamicin-containing ADC, gemtuzumab ozogamicin, which resulted in a postmarket dose fractionation. Although the inotuzumab ozogamicin dosing strategy was unique and successful at identifying an efficacious response-guided dosing regimen, this dosing regimen was based on only 3, 12, and 9 patients in the 1.2, 1.6, and 1.8 mg/m^2 dosing cohorts, respectively.[42] It remains uncertain whether it yielded the optimal dose for the entire population due to the safety signals seen in the phase III study and limited dosing range studied in the phase I setting. Thus, it is unclear whether or not a lower dose would optimize the benefit–risk profile for certain patients, especially those at high risk for VOD. Nevertheless, the inotuzumab ozogamicin adaptive dosing regimen based on response was found to be more efficacious than the standard of care, leading to inotuzumab ozogamicin's approval for the treatment of R/R ALL with the following two postmarketing requirements.[43,44] First, inotuzumab ozogamicin toxicity in patients with post–hematopoietic stem cell transplantation procedure should be further characterized in a real-world setting. Next, a randomized, multiple dose phase II clinical study to explore the exposure–response relationship in patients at high risk for AEs and to confirm the optimal dose for this population is being conducted. This ongoing study is comparing two dose levels of 1.2 and 1.8 mg/m^2 per 28-day dosing cycle in patients at high risk for developing VOD.[45]

Randomized dose-finding

Phase II/III studies are designed to assess primary clinical efficacy and safety. However, these studies generally do not provide data on multiple dose levels, which creates a major roadblock to dose optimization in oncology and immuno-oncology. This lack of multiple dose data limits researchers' ability to conduct robust exposure–response (E-R) analyses of long-term clinical safety and efficacy, and thus their ability to determine an optimized dose or regimen. For some of the therapeutic biologics in oncology, postmarketing studies that evaluate a higher dose cannot consistently confirm improved efficacy, even when an apparent E-R relationship for efficacy is observed at either the approved or late-stage clinical dose.[46–52] Specifically, time-varying CL, baseline disease burden, and disease progression/modification were identified as potential confounding factors which may lead to biased E-R relationships for efficacy from a single dose cohort and make a true flat relationship appear to be steep. Hence, an evaluation of multiple dose levels in a randomized study may result in the separation of baseline disease/demographic factors and drug exposure and their correlation reduced, thereby allowing for a more accurate estimation of the exposure-driven E-R relationship.

On the other hand, in the case of inotuzumab ozogamicin, the E-R analysis for efficacy identified a positive correlation between cumulative exposures after the first cycle of treatment (cAUCP1), C_{avg} and the probability of CR/CRi at the doses of 1.2, 1.6, and 1.8 mg/m^2. However, a statistically significant relationship was evident between cAUCP1 and the risk of Hepatic Event Adjudication Board -assessed VOD / sinusoidal obstruction syndrome. Given the limited number of patients tested at the 1.2 mg/m^2 dose ($N = 3$) and the very high rates of VODs including mortalities, the applicant was issued a postmarketing requirement to further optimize the inotuzumab ozogamicin dose consistent with the lowered VOD rates and early mortality observed with inotuzumab ozogamicin at the fractionated dosing regimen of 3 mg/m^2 on Days 1, 4, and 7 fractionated dosing vs. 9 mg/m^2.[40]

Therefore, ideally, a prospective study using multiple randomized dose levels and a sufficiently large sample size should maximize understanding of the benefit–risk profiles of multiple efficacious dose levels and their E-R relationships. This would provide critical support of dose selection and optimization. Two of the FDA-approved ADCs, fam-trastuzumab deruxtecan and belantamab mafodotin employed this strategy during phase II clinical trials.

Fam-trastuzumab deruxtecan uses a self-immolative, enzymatically cleavable peptide linker to combine humanized anti–human epidermal growth factor receptor 2 (HER2) antibody with a topoisomerase I inhibitor payload (DXd; an exatecan derivative). The MTD was not reached at the tested dose range of 0.8–8.0 mg/kg during a phase I dose escalation study of fam-trastuzumab deruxtecan performed in patients with HER2-positive advanced-unresectable or metastatic breast and gastric cancers who had been previously treated with trastuzumab emtansine or trastuzumab. However, dose responses were observed with most partial responses in patients treated with 5.4 mg/kg fam-trastuzumab deruxtecan or higher. While no apparent correlations between dose and overall occurrence of AEs were observed, a numerical increase in the grades 3/4 AEs were noted in the higher dose cohorts (5.4–8 mg/kg) compared with the lower dose cohorts. Based on the overall efficacy and safety data, the fam-trastuzumab deruxtecan doses of 5.4 mg/kg and 6.4 mg/kg were evaluated further in the expansion portion of the study.[53]

In the phase II study conducted to identify the recommended dose for HER2-positive, unresectable or metastatic breast cancer, patients who had received previous treatment with trastuzumab emtansine were randomized in a 1:1 ratio to receive either 5.4 mg/kg or 6.4 mg/kg doses of fam-trastuzumab deruxtecan.[54] Based on the exposure–efficacy analyses, a statistically significant relationship was found between fam-trastuzumab deruxtecan exposures (C_{trough}) and both overall response rates (ORRs) and best tumor response. There was a trend for higher progression-free survival (PFS) at higher fam-trastuzumab deruxtecan exposures but the relationship was not statistically significant. Statistically significant relationships were also found in the exposure–safety analysis between C_{max} and AUC of both fam-trastuzumab deruxtecan and DXd and key AEs (any grade interstitial lung disease, any grade or grade ≥3 anemia, any grade or grade ≥3 neutrophils/platelet count decreases). Additionally, significant relationships between fam-trastuzumab deruxtecan and DXd exposures and treatment-emergent adverse event (TEAE)–related dose reductions/discontinuations were observed.[54] The confirmed ORRs at 5.4 mg/kg and 6.4 mg/kg doses were 52.6 % (20/38) and 55.7% (34/61), and the model predicted 6-month PFS rates were ~ 87% and ~ 90% for the 5.4 mg/kg and 6.4 mg/kg doses, respectively. Overall, the 6.4-mg/kg dose was projected to have better efficacy, but also a higher risk of developing TEAEs or discontinuation / dose reduction due to TEAEs. Based on the predicted benefit–risk profile modeled

from exposure–response, exposure–safety, and pharmacokinetic analysis, 5.4 mg/kg Q3W was chosen as the recommended dose for continued development in HER2-positive breast cancer.[53–55]

Belantamab mafodotin is a humanized, afucosylated, anti–B-cell maturation antigen mAb conjugated to monomethyl auristatin F via a maleimidocaproyl linker. In the phase I study (DREAMM-1, $N = 73$) conducted in the heavily pretreated relapsed refractory multiple myeloma (R/R MM) patients, safety and efficacy were assessed with broad belantamab mafodotin doses ranging from 0.03 to 4.6 mg/kg Q3W IV. The 3.6 mg/kg dose was selected as the recommended phase II dose.[56]

In the subsequent pivotal phase II study (DREAMM-2), third-line and above (3L+) R/R MM patients received 2.5 mg/kg or 3.4 mg/kg belantamab mafodotin doses (randomized 1:1).[57] Although this study was not designed to compare belantamab mafodotin doses or address noninferiority, comparisons for efficacy and safety were performed using exploratory analyses. The probability of treatment response and PFS were not related to drug exposure after accounting for baseline disease factors, while the time to response was inversely related to belantamab mafodotin's C_{trough}. Higher belantamab mafodotin C_{trough} was associated with the increased probability of developing grade ≥2 or ≥3 ocular exam finding (OEF) and inversely correlated to time to onset of OEF. Baseline disease factors were also inversely associated with probability of OEF. Higher payload exposures (C_{max}) and lower baseline platelet count were associated with increased probability of ≥3 TCP. After accounting for patient and disease factors the DREAMM-2 study did not demonstrate an improvement in efficacy at higher exposure or dose based on an integrated evaluation of the E-R relationships and the increased probability of OEF and TCP. This supported a monotherapy dose of 2.5 mg/kg IV Q3W of belantamab mafodotin in R/R M/M patients.[58]

Conclusion

ADCs represent a rapidly evolving area of oncology drug development and hold significant promise. The strategy of conjugating a potent, nonspecific payload to an antibody dramatically improves the therapeutic window of drugs whose cytotoxicity would otherwise be untenable, allowing them to be used therapeutically. The FDA has already approved nine ADCs across the solid and hematological tumor indications. Several additional ADCs show promising clinical activity and expect FDA approval in the next one to two years. Following the great success of these ADCs, numerous innovative approaches (e.g., site-specific conjugation or novel payloads) have been implemented to further improve the therapeutic window, resulting in the "next-generation" ADCs. However, it is worth noting that the therapeutic window for these next-generation ADCs remains relatively narrow, especially when compared with other oncology drugs such as targeted therapies or checkpoint inhibitors. Maximum tolerated dose is often reached before ADCs achieve maximum efficacious dose, which poses a challenge to ADC dose optimization.

In this review, we have summarized multiple dosing strategies used for the FDA-approved ADCs that broaden the therapeutic window by mitigating the safety risks while maintaining efficacy. BW-based dose capping is an effective way to prevent the overdosing of heavier patients and to minimize the occurrence of AEs in these patients. Capping of treatment duration can effectively mitigate certain chronic AEs like PN that occur upon repeat dosing. Optimizing the dose schedule to a smaller and more frequent dose is a viable approach to reduce AE risks driven mainly by an ADC's C_{max} while maintaining efficacy. Response-guided dosing is an alternative approach for personalizing the ADC dose based on patients' response, although this approach usually requires fast onset (e.g., 21 days for inotuzumab ozogamicin) of response to enable this adaptive and individualized dosing approach. Finally, randomized dose-finding studies, especially for ADCs that demonstrate both efficacy and safety concerns across multiple doses, become increasingly important to identify an appropriate dose and schedule for late development and may increase the overall efficiency of clinical development. Many of these approaches employ the quantitative integration of clinical PK, PD, efficacy, and safety. A comprehensive evaluation of risk–benefit balance is needed to maximize the therapeutic window of each ADC to determine an optimal dosing regimen. Innovative dosing strategies learning continues especially for next-generation ADCs.

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CONFLICT OF INTEREST

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