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A Consideration of Fixed Dosing Versus Body Size-Based Dosing Strategies for Chimeric Antigen Receptor T-Cell Therapies

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CAR-T cell therapies, cellular kinetics, exposure-response models, fixed and body-weight-based dosing

Historically, body-size-based dosing has been utilized for many anticancer drugs. For instance, a common practice implementing body-surface-area (BSA)-based dosing was started decades ago for small molecule chemotherapies (eg, taxanes) with the hypothesis that large patients have a larger volume of distribution and a higher metabolizing activity, thus require a higher dose to achieve similar drug exposures to smaller patients.[1] Another typical body-size-based dosing can be exemplified by body-weight (BW)-based dosing for immune-oncology therapeutics (eg, PD-(L)1 inhibitors). These body-size-based dosing strategies are frequently employed in early phase trials, with a possible switch to fixed dosing later in clinical development or life-cycle management dependent on interpatient variability. Such a switch is often facilitated via population pharmacokinetic (popPK) modeling, exposure-safety, and exposure-efficacy simulations to demonstrate similarities in PK and benefit:risk profiles for the two dosing regimens (ie, body-size-based vs fixed dosing).[2–5] It is well established that for monoclonal antibodies, peptides, and other biologics, fixed dosing is as effective in controlling intersubject variability of drug exposure as body-size-based dosing given the body weight range (41–153 kg) in the studied adult patients.[6] Although operationally difficult and still in the exploratory stage, a measurement of body composition of lean mass (blood, muscle, and fatty tissue) by bioelectrical impedance analysis (BIA) or computed tomography (CT) cross-sectional imaging may provide accurate dosing for cancer patients while preventing dose-limiting toxicities.[7,8] With over two-fold variabilities in both fat and fat-free mass for BSA-based dosing in breast cancer patients, potential toxicities were associated with sarcopenic patients, while overweight or obese sarcopenic patients had an inferior outcome compared to normal weight patients with sarcopenia.[8] It was reported also that obese adult patients tolerated body-size-based dosing of chemotherapy in a similar way to nonobese patients.[9]

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The chimeric antigen receptor T-cell (CAR-T) therapies are customized "living drug" therapies involving the collection of T cells from the individual patient, the ex vivo re-engineering of the T cells in the laboratory to express CAR proteins on their surface, and the infusion of CAR-T cells back to the patient. The CAR constructs consisted of an extracellular antigen-recognizing single-chain variable fragment (scFv) (from an antibody sequence) fused to a transmembrane region and the intracellular signaling domains of CD3zeta and co-stimulatory domains (CD28 or 4-1BB). The engineered CAR-T cells can recognize and bind to specific antigens on the surface of cancer cells through the scFv domain, and expand/persist for a long period of time (activate intracellular signaling) to kill cancer cells and thus achieve clinical efficacy.[10] CAR-T therapies are an established treatment option demonstrating high rates of durable response in hematological malignancies[11] and show promising response rates in the solid tumor setting.[12] In the thriving field of chimeric antigen receptor (CAR) T-cell therapies, the factors contributing to selecting fixed versus body-size-based dosing remain unclear, which necessitates further examination using industrial and clinical development perspectives. We here particularly discuss whether fixed-dosing or body-size-based dosing should be recommended for CAR-T in the context of dosing experience, manufacturing, product characteristics, clinical safety, as well as cellular kinetics (CK)/exposure–response (E-R) models for CAR-T (Figure S1).

Dosing Experience and Approved CAR-T Products

BW, BSA, and fixed-dosing strategies have already been utilized in US FDA-approved/or developing CAR-T therapies. Tiasagenlecleucel used a BW-dosing strategy for pediatric patients ≤50 kg. Its approval for treating adult lymphoma patient was based on fixed dosing (BW range 38.4–186.7 kg). Axicabtagene ciloleucel and brexucabtagene autoleucel were authorized with BW dosing (BW range data unavailable), whilst lisocabtagene maraleucel (BW range 40.1–182.2 kg) and idecabtagene vicleucel (BW range 42.6–125.6 kg) were approved with fixed-dosing.[8] Most recently, approval for ciltacabtagene autoleucel recommended BW-based dosing (BW range data unavailable).

Both dosing strategies have been implemented in the investigation of CAR-T in the hematological (eg, anti-B-cell maturation antigen [BCMA]) and solid (eg, anti-glypican-3 [GPC-3]) tumor indications (Table 1). While promising, the success of CAR-T in hematological malignancies has yet to be replicated in solid tumors. Complicating factors for CAR-T therapy development in solid tumors include trafficking CAR-T, the immunosuppressive microenvironment within the tumor, and heightened risk of cytokine release syndrome (CRS).

Manufacturing, Product Characteristics, and Clinical Safety

Although manufacturing is amenable to any dosing strategy, for example with BW dosing vials are filled for a maximum weight estimate (or with the possibility of preparing a range of vial volumes in a similar way that a range of dose sizes is available for other types of medicines, but this might add more complexity and manufacturing cost) and only a fraction of the volume will be infused, autologous cell therapy presents unique challenges to manufacturing. First, some therapies may involve rare or hard-to-grow cells such as natural killer T cells. For a weight-based calculation, the option of overfill to accommodate the BW range of patients becomes difficult. Second, although pre-acquiring patient BW information may allow adjustment of the fill volume through a calculation and decision tree in the Production Batch Record, this adds a level of complexity that introduces possibilities for mistakes and slows the critical fill-and-freeze step. Fixed dosing makes CAR-T more accessible and cost-efficient along with improving manufacturing convenience and speed of production.[13,14]

Allogeneic "off-the-shelf" products can offer promising alternatives to autologous CAR-T therapies by reducing manufacturing steps/durations significantly. A fixed-dose allogeneic CAR-T might be a simpler and more convenient dosing strategy than BW-based,[13] applicable to a broader patient population, such as those with the rapidly progressing disease who commonly require bridging therapy between the time of apheresis and cell infusion due to the long manufacturing timelines of autologous products.

In addition to the above considerations, significant challenges hinder the development of robust models that can translate preclinical data into clinical CAR-T exposures (kinetics) and expected responses.[15] Unlike small molecule or biologics, CAR-T as "living" drugs exhibit unique kinetics (eg, CAR-T cells typically exhibit a lag time prior to expanding the cell population to a peak number, followed by a distribution phase and much longer persistent decline phase lasting several months to a couple of years) with high interpatient variability, for instances idecabtagene vicleucel or ciltacabtagene autoleucel transgene exposure parameters maximum observed analyte concentration (C_{max}) and area under the analyte concentration–time curve (AUC) from time 0 to 28 days ($AUC_{0\text{-}28d}$) had high interindividual variability (coefficient of variation [CV]% 126%–215% and 50%–124%, respectively). Causes of

Table 1. Summary of Six Approved CAR T-Cell Products and Ongoing CAR T Trials

Products	N	Target	Dose Type	Median Age (Range)	ORR	CR/VGPR	≥Gr3 CRS/Gr5 Events
Axicabtagene ciloleucel[a]	101	CD-19	Weight-based	58 (23–76)	72%	51%/–	13%/–
Brexucabtagene autoleucel[a]	60	CD-19	Weight-based	65 (38–79)	87%	62%/–	18%/–
Tiasagenlecleucel[a]	ALL: 63	CD-19	ALL (pediatrics): fixed for BW > 50 kg	ALL: 12 (3–23)	ALL:–	ALL: 83%/–	ALL: 49%/–
	DLBCL: 68		DLBCL: Fixed	DLBCL: 56 (22–74)	DLBCL: 50%	DLBCL: 32%/–	DLBCL: 23%/–
Lisocabtagene maraleucel[a]	256	CD-19	Fixed	63 (18–86)	73%	54%/–	4%/–
Idecabtagene vicleucel[a]	128	BCMA	Fixed	61 (33–78)	73%	31%/20%	6%/2%
Ciltacabtagene autoleucel[a]	97	BCMA	Weight-based	61 (43–78)	97%	67%/26%	5%/6%
C-CAR088	23	BCMA	Weight-based	60 (45–74)	96%	44%/48%	4%/0%
GC012F	16	BCMA	Weight-based	56 (27–71)	94%	56%/–	13%/0%
CT053	18	BCMA	Fixed	62 (36–78)	94%	28%/28%	0%/0%
P-BCMA-101	30	BCMA	Weight-based	60 (42–74)	65%	–/43% (VGPR+)	0%/0%
ALLO-715[b]	26	BCMA	Fixed	65 (46–76)	42%	–/23% (VGPR+)	0%/3%
GPC3 CAR-T 2 studies in China	13	GPC3	Weight-based for 8 patients; and fixed for 5 patients	51 (34–70)	15%	–/–	8%/8%
GPC3 CAR-T	3	GPC3	Surface area-based	–	–	–/–	67% neutropenia/–
BPX-601	23	PSCA	Weight-based	–	–	–/–	4%/–
PSCA CAR-T	–	PSCA	Fixed	–	–	–/–	–
CART-PSMA-TGFβRIIdn	8	PSMA	Surface area-based	–	–	–/–	–
Anti-mesothelin CAR-T	18	Mesothelin	Fixed	–	11%	–/–	–

ALL, acute lymphocytic leukemia; BCMA, B-cell maturation antigen; BW, body weight; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; GPC3, glypican-3; Gr, grade; ORR, objective response rate; r/r (or RR), relapsed/refractory; PSMA, prostate-specific membrane antigen; VGPR, very good partial response. –, data not available.

[a]US FDA-approved products.

[b]Allogeneic CAR-T product.

variability might include CAR constructs and functions, patient tumor burden and disease background, manufacturing variations, lymphodepletion, and CAR-T dosing regimens. After infusion, the infused CAR-T cell populations can expand, contract, and persist between patients in very different ways. The starting point (ie, initial infused CAR-T cell numbers or transgene levels) represents the dose received for each patient, while the expansion of the infused cell population to maximum cell numbers as well as the area under the expansion/contraction–time curve reflect CAR-T exposure parameters (C_{max} and AUC). It was acknowledged that conventional allometric scaling methods for cellular and gene therapy (CGT) products might be less precise as compared with small-molecule drugs, and traditional PK-pharmacodynamic correlations may not be possible, thus it might be difficult to identify an initial safe starting dose. The use of previous clinical experience with the CGT product or related products was thereby suggested (Considerations for the Design of Early-Phase Clinical Trials of CGT Products, FDA 2015). The recommendation of body-size-based dosing would need further clarification as many approved products and ongoing clinical studies report no significant relationship between body size metrics and CK, safety, or effectiveness.

Cellular Kinetics Models

The minireview by Huang et al summarizes clinical pharmacology aspects of first five approved CAR-T products without specific discussion on body size versus fixed-dosing strategies or the impact of body size on exposure or response.[11] The dose–exposure relationships are inconsistent across products. However, positive exposure–response relationships were observed for all five products in at least one indication. The CAR-T exposure is related to various factors such as tumor burden, depth of lymphodepleting chemotherapy, CAR-T phenotype, and patient comorbidities. For example, the CK curves of lisocabtagene maraleucel overlapped across 50, 100, and 150 million cells dose levels, and no dose–exposure or dose–efficacy relationships were identified.[16] BW was not identified as a significant covariate.[16] Although there was a positive trend for the E-R between CAR-T cell growth and tumor response, FDA evaluation (lisocabtagene maraleucel BLA 125714 Clinical Pharmacology Review document) suggested it should not be interpreted as causally connected between dose and response, given the observed flat dose–exposure–response relationship. Further exploratory analyses indicated that the CD4/CD8 ratio is an important factor for both efficacy (eg, best overall response) and safety (eg, CRS and neurotoxicity [NT]). Several cytokines seemed to be closely related to CRS but not strongly associated with response status (eg, IFNγ, IL2, and IL4, etc. show a greater increase in patients with CRS while a greater decrease in TGFβ1 was observed in patients with CRS). The first approval for BCMA-targeting CAR-T is idecabtagene vicleucel. Pooled data from two idecabtagene vicleucel studies demonstrated positive relationships for both dose–response (objective response rate [ORR]) and dose–exposure (C_{max}, T_{max} − T cell expansion rate).[11] A positive E-R relationship was observed, although a causal effect may be obscured since exposure might also be affected by clinical outcomes and other confounding effects. A broader range of dose levels was tested (150 up to 800 million cells fixed dosing) as compared with lisocabtagene maraleucel.[16] Female patients had better responses than males at the same dose level, with the effect of BW on efficacy considered secondary to gender. The recommended dose of idecabtagene vicleucel is 450 million cells, but a minimum threshold of 300 million cells is required for efficacy. For the products axicabtagene ciloleucel/brexucabtagene autoleucel using BW-based dosing, flow cytometry or quantitative polymerase chain reaction (qPCR) assays characterized CK and found that exposure was numerically higher for patients age <65 years versus those ≥65 years, although confounding factors (eg, small sample size, tumor burden) should be considered. C_{max} and $AUC_{0\text{-}28d}$ were higher in responders versus nonresponders, and in subjects with grade 3+ CRS/NT versus those with grade <3 CRS/NT events. At a dose of 0.5×10^6 CAR-T cells/kg, the C_{max} and $AUC_{0\text{-}28d}$ of brexucabtagene autoleucel were approximately 60% of that in subjects treated at a dose of 2×10^6 CAR-T cells/kg, exhibiting a potential underexposure.

Exposure–Response Relationships

There are a few publications on clinical CK–pharmacodynamics modeling for Tiasagenlecleucel.[17–19] In addition, Liu et al[20] described a CK model with distribution, expansion, contraction, and persistence phases using linear functions based on 207 hematological or solid tumor patients' data. BW, unlike baseline tumor burden, was not a significant covariate for CAR-T cell expansion/contraction. This is consistent with the population CK in lisocabtagene maraleucel, where age but not BW was identified as a significant covariate on C_{max} (maximum transgene levels) and doubling time for cell expansion. Compared to a 63-year-old patient, the magnitude of age impact on C_{max} could be a 2.5-fold change for an 18-year-old patient versus a 0.25-fold change for someone aged 83. Additionally, an 18 or 83-year-old patient has a

0.7- or 1.2-fold change, respectively, of doubling time for cell expansion, representing a substantially faster expansion rate for younger patients. Other significant covariates were baseline tumor burden on HL_α (decline in half-life in initial contraction α phase before a long persistent phase), tocilizumab/corticosteroid use on C_{max} and HL_α, as well as manufacturing process on lag time from CAR-T post-infusion to the start of an expansion. The impact of BW on CK parameters is relatively smaller than the factors discussed above.[20]

Additionally, Singh et al[21] reported a multiscale mechanistic model for anti-BCMA CAR-T products and indicated that a minimally required number of cells (a 150 million cell threshold) could be established for efficacy based on pharmacodynamic biomarkers serum BCMA. These results thus further support fixed dosing. Furthermore, ciltacabtagene autoleucel data indicated that a two-compartment model and a chain of four transit compartments with a lag time can adequately describe the observed transgene-time data, and none of the investigated subject demographics, baseline characteristics including BW (age, sex, race, hepatic, or renal impairment), or manufactured product characteristics had a statistically significant effect on population CK model parameters in the covariate analysis.

Conclusions

Overall, this analysis suggests that the impact of body size (BW or BSA) on interpatient variability of CK for an adult cancer patient is small relative to other variability contributors in CAR-T cell expansion and contraction. For pediatric patients (BW < 50 kg), BW-based dosing is recommended most likely due to age as a significant covariate for cell doubling time (much faster cell doubling for young patients) and likely due to safety concerns.[20] Further evaluation of body size impact based on accumulating clinical data is needed to justify the appropriate dosing strategy for specific CAR-T therapy in treating adult patients with hematological or solid tumors.

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Conflicts of Interest

J.Z.H., M.V., N.S., and R.K. are prior employees of AstraZeneca. H.W., K.L., S.R., F.R., R.W., R.S., A.P., and M.G. are employees and shareholders of AstraZeneca.

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