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Dose–response correlation for CAR-T cells: a systematic review of clinical studies

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ABSTRACT

The potential of chimeric antigen receptor (CAR) T cells to successfully treat hematological cancers is widely recognized. Multiple CAR-T cell therapies are currently under clinical development, with most in early stage, during which dose selection is a key goal. The objective of this review is to address the question of dose-dependent effects on response and/or toxicity from available CAR-T cell clinical trial data. For that purpose, systematic literature review of studies published between January 2010 and May 2022 was performed on PubMed and Embase to search clinical studies that evaluated CAR-T cells for hematological cancers. Studies published in English were considered. Studies in children (age <18 years), solid tumors, bispecific CAR-T cells and CAR-T cell cocktails were excluded. As a result, a total of 74 studies met the inclusion criteria. Thirty-nine studies tested multiple dose levels of CAR-T cells with at least >1 patient at each dose level. Thirteen studies observed dose-related increase in disease response and 23 studies observed dose-related increase in toxicity across a median of three dose levels. Optimal clinical efficacy was seen at doses 50–100 million cells for anti-CD19 CAR-T cells and >100 million cells for anti-BCMA CAR-T cells in majority of studies. The findings suggest, for a given construct, there exists a dose at which a threshold of optimal efficacy occurs. Dose escalation may reveal increasing objective response rates (ORRs) until that threshold is reached. However, when ORR starts to plateau despite increasing dose, further dose escalation is unlikely to result in improved ORR but is likely to result in higher incidence and/or severity of mechanistically related adverse events.

INTRODUCTION

Cancer immunotherapy has made giant strides in the past 10 years with the development of multiple strategies including tumor-specific chimeric antigen receptor (CAR-) T cell therapies, monoclonal antibodies targeting checkpoint blockers and oncolytic viruses.[1–6] CAR-T cell therapy demonstrated impressive results in hematological cancers with objective response rates (ORRs) as high as 100% noted in some studies.[7 8] To date, six CAR-T cell therapies including axicabtagene ciloleucel (axi-cel), brexucabtagene autoleucel (brexu-cel), tisagenlecleucel (tisa-cel), lisocabtagene maraleucel (liso-cel), idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) have been approved by the US Food and Drug Administration (FDA) for different hematological malignancies with wide-ranging doses such as 60–600 million cells for tisa-cel, 50–110 million cells for liso-cel and 2 million cells/kg body weight for axi-cel (table 1). While currently available CAR-T cell therapies showed excellent response rates, limitations such as durability of efficacy, incidence of adverse events, including cytokine release syndrome (CRS) and neurotoxicity, and production-related issues warrant continued advancement of novel CAR-T cell therapies.

To address the limitations and improve treatment outcomes, several CAR-T cell therapies of autologous and allogeneic origin are currently being developed, with most in early stages of clinical development. Dose selection is a critical determinant of the success of any cancer therapeutic, including cell therapies. Recommendation of subtherapeutic dose for the pivotal study could result in lower efficacy, whereas excessive dose could result in higher incidence and/or greater severity of adverse events. Typically phase 1 dose escalation studies are performed to recommend possible effective dose and maximum tolerated dose (MTD). Unless MTD is reached during the phase 1 study, determination of further dose escalation impact on efficacy and/or the incidence or severity of adverse events may not be possible. Dose selection may be more difficult for therapies like CAR-T cells, which cannot be described by typical principles of clinical pharmacology, such as receptor occupancy and elimination kinetics.

Currently, initial dose recommendations are made based on preclinical models and empiric data from previous relevant studies with similar constructs in the same cancer type. However, the question of possible increase in efficacy with higher dose continues to remain in clinical development discussions because there is conflicting evidence on CAR-T cell

Table 1 US Food and Drug Administration (FDA)-approved CAR-T cell therapies (current as of February 2022)

CAR-T therapy	Target	Indication	Dose
Axicabtagene ciloleucel	CD19	Relapsed and refractory B cell lymphoma including DLBCL and follicular lymphoma after two or more lines of therapy	2 million cells/kg body weight with a maximum of 200 million cells
Brexucabtagene autoleucel	CD19	Relapsed and refractory mantle cell lymphoma	2 million cells/kg body weight with a maximum of 200 million cells
		Relapsed or refractory B cell precursor acute lymphoblastic leukemia	1 million cells/kg body weight with a maximum of 100 million cells
Tisagenlecleucel	CD19	Children and young adults (up to 25 years of age) with B cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse	0.2–5 million cells/kg body weight, if the patient body weight is ≤50 kg; 10–250 million cells if the patient body weight is >50 kg
		Adults with relapsed or refractory B cell lymphoma after two or more lines of systemic therapy	60–600 million cells
Lisocabtagene maraleucel	CD19	Relapsed and refractory B cell lymphoma including DLBCL after two or more lines of therapy	50–110 million cells consisting of 1:1 ratio of CAR^+ CD4 and CD8 cells
Idecabtagene vicleucel	BCMA	Multiple myeloma after four or more lines of therapy	300–460 million cells
Ciltacabtagene autoleucel	BCMA	Multiple myeloma after four or more lines of therapy	0.5–1 million cells/kg body weight with a maximum of 100 million cells

CAR, chimeric antigen receptor; DLBCL, diffuse large B cell lymphoma.

dose–response. Positive correlation between increased response and higher dose levels was reported in some studies,[9 10] whereas no correlation was seen and efficacy was similar at all dose levels in other studies.[11] This review aimed to perform systematic literature review of CAR-T cell studies in adult patients with hematological malignancies and summarize the findings on dose–efficacy and dose–safety correlations. The main question the review intended to address was if there is a correlation between dose of CAR-T cell therapy and response in patients and if the efficacy increases or decreases in a dose-dependent fashion. Second, the study aimed to understand if the incidence or severity of cytokine release syndrome (CRS) and neurotoxicity was impacted by dose. Finally, the study aimed to document the findings on predictors of response including peak expansion (Cmax), area under the expansion curve (AUC) and tumor burden.

METHODS

This systematic review followed the guidelines defined by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement.[12]

Search criteria

The following search terms were used in the literature search for related articles: “CAR”, “chimeric antigen receptor”, “CAR-T cell”, “acute lymphoblastic leukemia”, “ALL”, “diffuse large B-cell lymphoma”, “DLBCL”, “multiple myeloma” and “MM”. Searches were conducted on PubMed and Embase in August 2021 and November 2021, respectively. A total of seven searches were conducted on each database: (1) “CAR” or “chimeric antigen receptor”; (2) “CAR-T cell” and “acute lymphoblastic leukemia” or “ALL”; (3) “CAR-T cell” and “diffuse large B-cell lymphoma” or “DLBCL”; (4) “CAR-T cell” and “multiple myeloma” or “MM”; (5) “chimeric antigen receptor” and “acute lymphoblastic leukemia”; (6) “chimeric antigen receptor” and “diffuse large B-cell lymphoma”; and (7) “chimeric antigen receptor” and “multiple myeloma”.

Eligibility

All clinical prospective and retrospective studies reporting outcomes in adult patients (age ≥18 years) with hematological malignancies including acute lymphoblastic leukemia (ALL), diffuse large B cell lymphoma (DLBCL) and multiple myeloma (MM) met the inclusion criteria for consideration. Studies were excluded if they met any of the following exclusion criteria: (1) articles reported in languages other than English; (2) conference presentations and abstracts; (3) studies that did not use lymphodepletion regimen; (4) studies in children; (5) studies in solid tumors; (6) studies using bispecific CAR-T cells; (7) studies using CAR-T cell cocktails; (8) studies using bispecific antibodies; (9) studies using antibody drug conjugates; (10) articles reporting additional outcomes/post hoc analyses of previously published study; (11) preclinical studies; (12) systematic literature review articles; and (13) review articles. Bispecific CAR-T cells, solid tumors and studies in children were excluded from the review because the kinetics, efficacy and safety can be comparatively different.

Data extraction

Studies meeting the eligibility criteria were screened based on their title, abstract and full text by two independent reviewers. Reasons for excluding studies were recorded, and included studies were cross checked prior to data extraction such that any discrepancy arising between the two reviewers was resolved through discussion. The following data were extracted from each study's full text: study details (author name, year of publication and country), patient characteristics (number of patients, cancer subtype, lines of prior therapy and tumor burden), CAR-T cell details (dose and regimen, target antigen, costimulatory domains, gene transfer method, generation of CAR-T cells and persistence of CAR-T cells), efficacy outcomes (overall survival (OS); progression-free survival (PFS); objective response rate (ORR); complete response rate (CRR); onset of response, duration of response (DoR), and markers of response and safety outcomes (CRS and neurotoxicity, onset of CRS/neurotoxicity).

Studies that reported outcomes from multiple doses of CAR-T cells were identified, and studies in which at least 50 patients received CAR-T therapy were prioritized. Dose was calculated for 70 kg for studies that used body weight-based dose and for 1.6 m^2 for studies that used body surface area-based dose to convert to a flat dose value in order to compare the dose across studies.

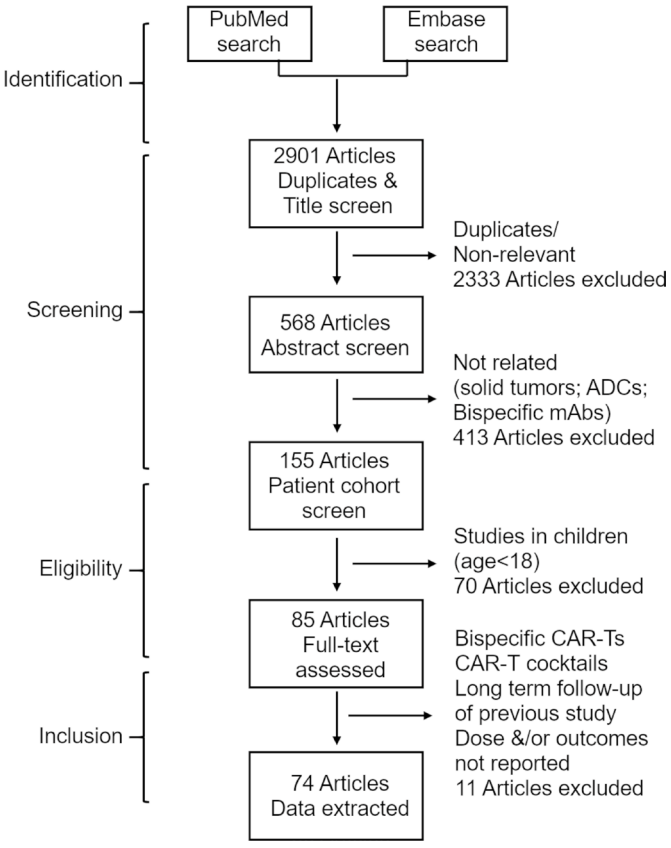

Figure 1 Study flow and selection of articles. CAR, chimeric antigen receptor.

RESULTS

Characteristics of selected studies

Literature search for clinical articles published between 1 January 2010 and 15 May 2022 identified 2901 papers on CAR-T cells. After removing duplicates and screening for relevant articles based on title, abstract and then full text by two reviewers, 74 articles were selected for systematic review and data extraction (figure 1).[13–66] Among the included studies, 19 (26%) studies had at least 50 patients treated, and 55 (74%) studies had <50 patients (online supplemental table S1). Quality of included studies was assessed using the guidelines for non-randomized single-arm studies (online supplemental table S2).[67–70] Majority of the studies included patients with ALL (n=30, 40%) or DLBCL (n=21, 28%) or MM (n=17, 23%). In total, 3109 patients with hematological cancers were treated including 927 (30%) DLBCL patients, 1054 (34%) B-ALL patients and 501 (16%) MM patients.

Multiple dose levels of CAR-T cells with >1 patient at each dose level were tested in 39 studies (table 2) including 9 (23%) studies with cohort size of at least 50 patients and 36 (92%) studies with cohort size of at least 10 patients. The TRANSCEND study by Abramson *et al*[11] in patients with large B cell lymphoma was the largest study with 269 patients evaluating three dose levels of treatment. Majority of the multidose studies targeted CD19 (26/39; 67%) and had single intracellular domain (33/39; 85%). Intracellular signaling domain included 4–1-BB in 19 (49%) studies, CD28 in 13 studies (33%), 4–1-BB and CD28 in 2 (5%) studies and CD28 and CD27 or OX40 in 2 (5%) studies (table 2).

Factors associated with response and incidence of CRS and neurotoxicity

Dose

To evaluate the dose–response association, studies that tested at least two dose levels and had more than one patient per dose level were included in the first step. Determination of CAR-T cell dose varied across studies, and flat dose of fixed number of cells were given in some studies, whereas other studies dosed patients on cells per kilogram (kg) body weight or cells per body surface area. To compare the dose across studies, dose was normalized and converted to flat dose by calculating the dose for 70 kg body weight or for 1.6 m^2 for studies that used body weight-based dose and body surface area-based dose, respectively. Out of 39 studies that tested at least two dose levels of CAR-T cells, association between dose administered and ORR/CRR (efficacy) was observed in 13 (33%) studies (table 2). When the studies with cohort size of at least 50 patients were compared (n=9), one study reported clear increase in response at higher doses,[10] two studies reported increase in response from DL1 to DL2 but no further increase at DL3[71 72] and one study observed positive correlation between dose and response in patients who had SD or PD at the time of infusion.[73] Intriguingly, the ORR and/or CR rate tended

Table 2 Summary of studies evaluating multiple dose levels

First author	Indication	Target	Signal domain	Dose* (million cells)	Response higher at higher dose	Toxicity higher at higher dose
Bishop *et al*[73]	LBCL	CD19	4–1-BB	Range: 40–590 (response correlation assessed per 100 million increments in dose)	Y	NR
Abramson *et al*[11]	DLBCL	CD19	4–1-BB	DL1: 50; DL2: 100; DL3: 150	N	NR
Zhang *et al*[77]	B-ALL	CD19	4–1-BB & CD28	Range: 1.4–371 DL1: <21 DL2: ≥21	N	N
Munshi *et al*[10]	MM	BCMA	4–1-BB	DL1: 150; DL2: 300; DL3: 450	Y	Y
Fowler *et al*[74]	FL	CD19	4–1-BB	Range: 60–600†	N	Y
Ying *et al*[75]	B-cell lymphoma	CD19	4–1-BB	100 or 150	N	Y
Zhao *et al*[71]	MM	BCMA	CD28	Range: 4.9 to 147†	Y	Y
Shah *et al*[72]	B-ALL	CD19	CD28	DL1: 35; DL2: 70; DL3: 140	Y	Y
Park *et al*[76]	B-ALL	CD19	CD28	DL1: 70; DL2: 210	N	NR
Ramos *et al*[43]	HL	CD30	No data	DL1: 32; DL2: 160; DL3: 320	N	N
Frey *et al*[30]	B-ALL	CD19	4–1-BB	DL1: 50; DL2: 500	Y	Y
Raje *et al*[42]	MM	BCMA	4–1-BB	DL1: 150; DL2: 450	Y	Y
Turtle *et al*[54]	NHL	CD19	4–1-BB	DL1: 14; DL2: 140; DL3: 1400	N	Y
Frey *et al*[29]	CLL	CD19	4–1-BB	50 or 500	Y	Y
Li *et al*[38]	MM	BCMA	CD28	Range: 378–1750 DL1: ≤784; DL2: >784	N	N
Turtle *et al*[53]	B-ALL	CD19	4–1-BB	DL1: 14; DL2: 140; DL3: 1400	N	Y
Ying *et al*[64]	B cell lymphoma	CD19	4–1-BB	DL1: 3–6; DL2: 60–190; DL3: 200–400	Y	N
Tu *et al*[52]	B-ALL	CD19	CD28 and CD27	Range: 6.2–280 DL1: <35 DL2: ≥35	N	Y
Turtle *et al*[55]	CLL	CD19	4–1-BB	DL1: 14; DL2: 140; DL3: 1400	N	Y
Geyer *et al*[32]	CLL	CD19	CD28	DL1: <700; DL2: >700	N	N
Brudno *et al*[17]	DLBCL	CD19	CD28	DL1: 46.2; DL2: 140; DL3: 420	N	N
Cui *et al*[24]	DLBCL	CD19	No data	Range: 70–490 DL1‡: <140; DL2‡: 140–<280; DL3‡: ≥280	N	Y
Wang *et al*[56]	HL	CD30	4–1-BB	Range: 770–1470§	N	N
Wang *et al*[57]	MM	BCMA	4–1-BB	DL1: 70; DL2: 210; DL3: 420	N	Y
Cornell *et al*[22]	MM	BCMA	CD28	DL1: 30; DL2: 100; DL3: 300; DL4: 1000	N	Y
Wang *et al*[59]	NHL	CD19	CD28	DL1: 25; DL2: 50; DL3: 100; DL4: 200	N	Y
Ramos *et al*[44]	B-ALL	K-LIGHT CHAIN	CD28	Range: 32–320§	N	N

Continued

Table 2 Continued

First author	Indication	Target	Signal domain	Dose* (million cells)	Response higher at higher dose	Toxicity higher at higher dose
Hu *et al*[35]	B-ALL	CD19	4–1-BB	Range: 77–686¶	N	N
Porter *et al*[41]	B-ALL	CD19	4–1-BB	Range: 14–1100†	N	N
Frigault *et al*[92]	MM	BCMA	41BB and CD3	DL1: 100; DL2: 300	N	Y
Baumeister *et al*[16]	AML	MICA/MICB	NKG2D	DL1: 0.738; DL2: 2.15; DL3: 6.92; DL4: 24.5	N	N
Ali *et al*[13]	MM	BCMA	CD28	DL1: 21; DL2: 70; DL3: 210; DL4: 630	Y	Y
Enblad *et al*[26]	Lymphoma	CD19	4–1-BB and CD28	DL1: 32; DL2: 160; DL3: 320	N	Y
Yan *et al*[63]	NHL	CD19	4–1-BB	DL1: 25; DL2: 50; DL3: 100	N	NR
Magnani *et al*[39]	B-ALL	CD19	CD28 and OX40	DL1: 70; DL2: 210; DL3: 525; DL4: 1050	Y	y
Geyer *et al*[31]	CLL	CD19	CD28	DL1: 210; DL2: 700; DL3: 2100	N	Y
Cruz *et al*[23]	B-ALL	CD19	CD28	DL1‡: 19–34; DL2‡: 58–110	Y	Y
Kochenderfer *et al*[37]	CLL	CD19	CD28	DL1‡: 21; DL2‡: 77–91; DL3‡: 119–210	Y	NR
Cohen *et al*[21]	MM	BCMA	4–1-BB	DL1**: 10–50; DL2, 100–500	Y	Y

*Calculated for 70 kg or 1.6 m^2 if dose was not flat.
†Granular dose details not provided but text described correlation (or lack of) details.
‡Dose categories were assigned from the dose range used in the study.
§Dose was not categorized by authors, and categories were not assigned for this study because overall response rate was very low.
¶Dose was not categorized by authors, and categories were not assigned for this study because overall response rate was high and occurred at all doses.
**Study included a cohort without lymphodepletion, which was excluded.
N, no; NR, not reported; Y, yes.

to be slightly better in the lower dose level cohorts in the studies that reported no correlation between dose and disease response (table 2, online supplemental table S3).

Within the studies that showed association between dose and ORR, the starting dose was comparatively lower (<30 million cells),[13 29 30 37 66 72] whereas the studies that showed no association between dose and disease response, the starting dose or DL1 was over 50 million cells.[11 74–76] The study by Zhao *et al* used a lower DL1 (21 million cells for 70 kg) and concluded that there was no association between CAR-T cell dose and response. However, authors discussed that only 20% (n=2/10) of patients in the DL1 group achieved PR or more, which was lower compared with other dose levels in the study. Similarly, DL1 in the Zuma-3 study[72] observed a positive dose response between DL1 (35 million cells for 70 kg) and DL2 (70 million cells for 70 kg) but did not see further increase in ORR in DL3 (140 million cells for 70 kg) cohort. While inconclusive, this suggests that very low doses of CAR T cells may not reach the threshold of full clinical activity which, when reached, results in maximal ORR/CR that cannot be improved on with increasing dose. In contrast, DL1 in the ide-cel pivotal study was 150 million cells[10] and the ORR as well as CR/sCR rate increased from DL1 to DL2 (300 million cells) and to DL3 (450 million cells) indicating that in cases where optimal clinical activity is not achieved at 100–150 million cells, further increase may increase the ORR.

To evaluate if there were any possible differences in association due to difference in target antigen or intracellular domains, studies that evaluated multiple doses were separated based on target antigen and on intracellular domains and the dose–response and dose–safety association was evaluated. As illustrated in figure 2, 8/26 (31%) studies targeting CD19 and 5/9 (55%) studies targeting BCMA noted a positive correlation between dose and ORR/CRR. Similar results were seen (figure 2) when studies were categorized based on intracellular signaling domain (single vs dual) and type of intracellular signaling domain (4–1-BB vs CD28). Interestingly, the trends seen when studies were separated based on antigen or signaling domain were in line with the trend seen with entire cohort. Association between dose–response was mainly at doses below the threshold of optimal clinical activity, but when optimal clinical activity was reached, further escalation increased toxicity without increasing ORR.

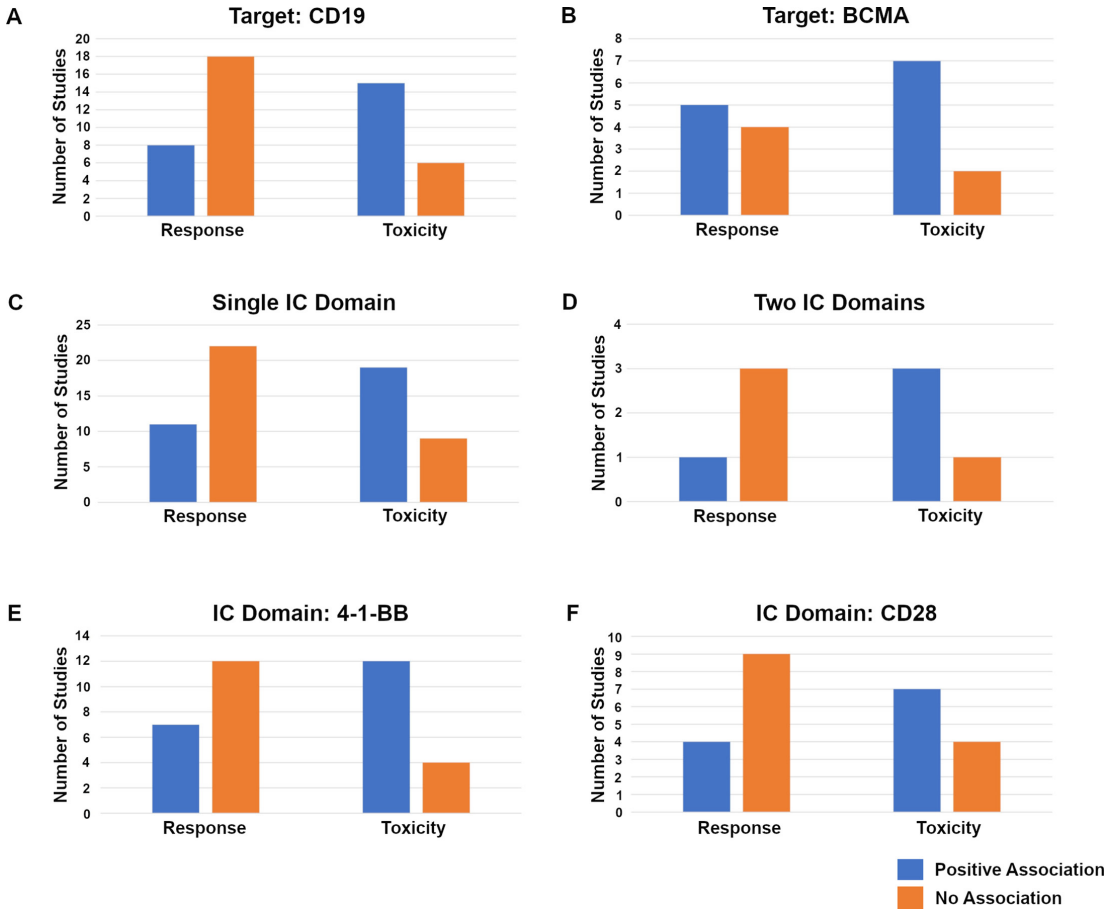

Figure 2 Response and toxicity association with dose in studies categorized by (A) CAR-T cells targeting CD19, (B) CAR-T cells targeting BCMA, (C) CAR-T cells with single intracellular (IC) domain, (D) CAR-T cells with two IC domains, (E) CAR-T cells with 4–1-BB IC domain and (F) CAR-T cells with CD28 IC domain. Positive association with dose was recorded as yes or no.

Dose–safety association was less frequently explored or reported compared with dose–response association. Out of the 39 studies that commented on dose–response correlation, 34 (87%) studies either commented on incidence and/or severity of CAR-T related adverse events including CRS and immune cell associated neurotoxicity syndrome (ICANS) or reported the adverse events (AEs) separately at different dose levels. Increased incidence and/or severity of CRS/ICANS was observed in 23 (68%) studies, and 11 (32%) studies noted no association between dose and toxicity (table 2). Out of 11 studies with cohort size over 50 patients, seven (64%) studies observed higher adverse events,[10 71 72 75] one (9%) study noted no association with dose[77] and three (27%) studies did not comment on dose–safety association.[11 76] Top DL varied widely in the studies that showed direct correlation between dose and adverse events with dose administered ranging between 110 million cells and 1000 million cells (table 2 and online supplemental table S3). Among the 11 studies that showed no association between dose and adverse events, split or fractionated dosing was used to mitigate adverse events in four (36%) studies[32 35 38 64] and ORR was also low in three (27%) studies.[16 44 56]

CAR-T cell expansion (AUC) and peak (Cmax)

Majority of the studies did not report CAR-T cell pharmacokinetics (PKs) parameters (AUC and Cmax) at individual dose levels. PK data reported in the studies were extracted and listed in online supplemental table S4. Disease response, adverse event incidence and adverse event severity were clearly associated with CAR-T cell expansion (see 'Findings on association with dose' column in table 2 and online supplemental table S3). Almost all studies that reported the factors associated with response noted that the disease response and/or CRS incidence or severity correlated directly with AUC or Cmax of CAR-T cells. Even in the studies that did not see a correlation between dose and disease response,[11 76] CAR-T cell PK was shown to be directly associated with response and/or safety.

In contrast, the association between dose and pharmacokinetic parameters was not clear. Majority of the studies (19/39; 49%) that tested multiple doses, either did not report PK or did not report PK separately for each DL. Among the studies that reported granular details of PK, positive correlation between dose and AUC and/or Cmax was observed in eight studies, and no correlation was noted in 11 studies (see 'Findings on association with dose' column in table 2 and online supplemental table S3).

Time to peak expansion and onset of response

As the CAR-T cell expansion can translate into tumor cell cytotoxicity, data from studies reporting time to peak

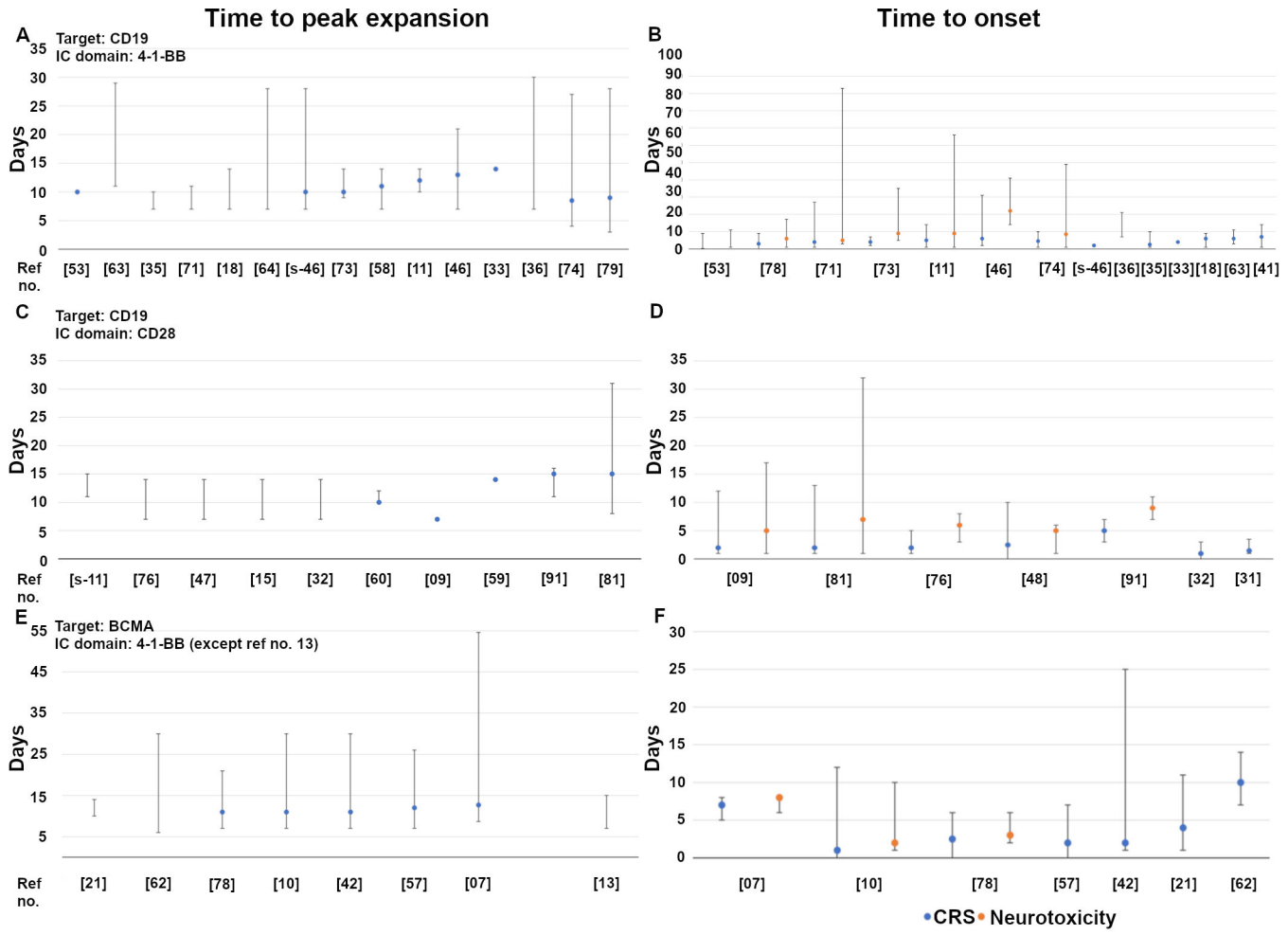

Figure 3 Time to peak expansion (left panels), onset of CRS and ICANS (right panels) in the CAR-T cells studies targeting (A and B) CD19 with 4–1-BB as intracellular signal, (C and D) CD19 with CD28 as intracellular signal and (E and F) BCMA with 4–1-BB as intracellular signal, except ref no. 13 has CD28 as intracellular signal. Markers represent median values, and error bars represent range (min–max) or IQR. Studies that reported only range are represented without markers. Detailed information is included in online supplemental table S5. CAR, chimeric antigen receptor; CRS, cytokine release syndrome.

expansion and onset of response (efficacy/safety events) were extracted (online supplemental table S5; figure 3). Fifty-two (70%) studies reported the time to peak CAR T-cell expansion and/or response including 11 studies with cohort size over 50 patients.[10 11 71 72 74–77] However, studies reported the onset times for the entire cohort; granular details at different dose levels were not reported. Interestingly, time to peak expansion in peripheral blood was comparable across all studies (7–14 days) even though doses varied. Similarly, median time to response (1 month), CRS events (1–7 days) and neurotoxicity events (2–12 days) were comparable across all studies. However, it should be noted that median time to response is limited to the first evaluation of response, which typically occurs at 1 month across all studies.

Tumor burden

Twenty-eight (38%) studies reported details of tumor burden at the time of treatment and its correlation with disease response and/or incidence/severity of CRS and neurotoxicity (online supplemental table S6).[9–11 42 75 76 78–81] High tumor burden was seen to be associated with lower response rates in majority of the studies (n=15; 54%) and was found to be associated with better response rate only in two (7%) studies.[25 80] The association between tumor burden and adverse event incidence or severity was reported in 14 (50%) studies: nine (32%) studies observed that high tumor burden was associated with higher incidence and/or severity of CRS and neurotoxicity, whereas five (18%) studies noted no difference (online supplemental table S6). Interestingly, studies by Turtle *et al* and Park *et al* used bone marrow tumor burden-based risk adoptive dosing strategy and noted that the approach reduced the toxicity of treatment.[53 76]

DISCUSSION

Current systematic review aimed to address a critical question in the early clinical development of CAR-T cells. Previous systematic reviews mainly summarized efficacy and/or safety outcomes or biomarkers associated

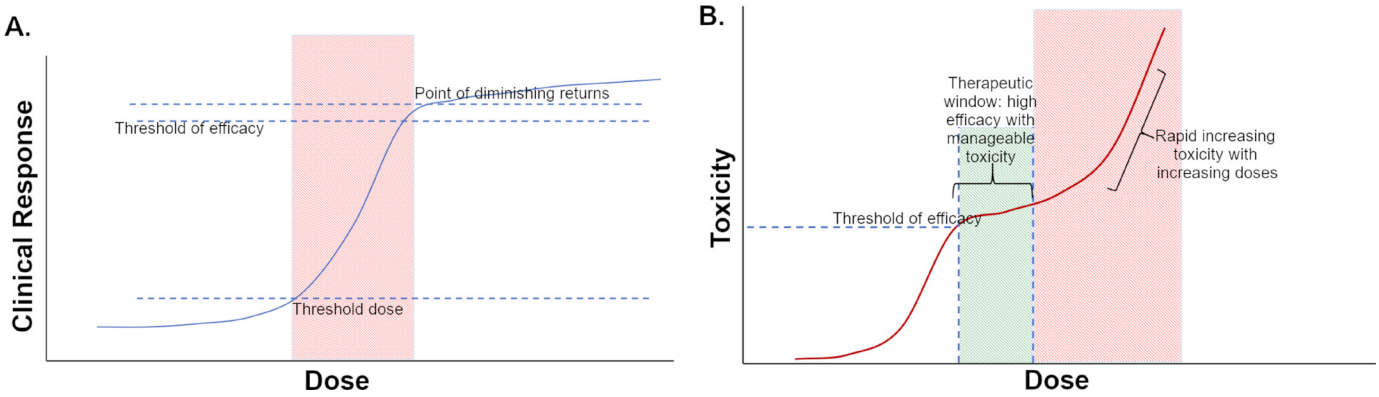

Figure 4 Model showing dose–response (A) and dose–toxicity (B) correlation of CAR-T cells. Increments in response can be seen when dose increments are made at lower doses (<50 million cells approximately). Increase in response is associated with increase in frequency of adverse events (CRS and ICANS), but the toxicity is manageable with standard treatment at threshold efficacy. Further increase in dose (>150 million cells approximately) beyond threshold efficacy could only have marginal increase in efficacy but could lead to significant increase in toxicity of CAR-T cells manifested as increased severity of adverse events. CAR, chimeric antigen receptor; CRS, cytokine release syndrome.

with safety outcomes for a specific CAR-T cell therapy or a specific indication,[82–89] but the correlation between dose and related factors and response was not studied. To derive from the combined knowledge of all relevant clinical studies, all CAR-T cells therapies for hematological cancers were analyzed together for correlations and then analyzed separately based on target antigens as well as intracellular domains. The review did not pool the efficacy or safety data across the studies. Instead, outcomes of each study were analyzed individually, and positive correlations or lack of correlations between dose and ORR/CRR, dose and toxicity were noted first, followed by overall assessment of correlation between dose and response (table 2, figure 2). This approach ensured that each study had its own comparative cohorts and thereby accounted for the possible differences in target antigens and CAR-T cell products.

In response to question of whether there is a dose-related increase in disease response to CAR-T cells, the results show that dose and disease response association was mainly seen when optimal clinical efficacy (defined based on the outcomes from the studies as >70% ORR) was not achieved at lower doses. The studies that did not show association (table 2 and online supplemental table S3) either had a very good overall response rate or had a poor overall response rate indicating that further dose escalation may not result in increased response when the response rates are very high (80%–100%) or very low (0–20%) due to intrinsic product attributes affecting cell expansion kinetics. Our findings also noted a general trend in dose required to achieve optimal clinical efficacy. Majority of anti-CD19 CAR-T cell studies achieved optimal clinical efficacy (>70% ORR) at doses between 50 and 100 million cells (table 2 and online supplemental table S3). Comparatively higher doses (>100 million cells) were needed to achieve optimal clinical efficacy for majority of anti-BCMA CAR-T cell studies (table 2 and online supplemental table S3), but it is to be noted that some anti-BCMA CAR-T cells like cilta-cel achieved optimal clinical efficacy at lower dose (<100 million cells) and did not see further increase in response at doses above 100 million cells.[71] The differences in dose required to achieve optimal clinical efficacy between anti-CD19 and anti-BCMA CAR-T cells are possibly due to differences in the target antigen expression on tumor cells or CAR-T cell product attributes. Similarly, the differences in optimal clinical efficacy dose between CAR-T cells targeting same antigen are possibly due to product characteristics such as CAR expression per cell, proportion of CAR+ cells in the final product and viability of CAR+ cells.

In contrast to dose and disease response association, incidence and/or severity of CAR-T cell-related adverse events including CRS and neurotoxicity was associated with the dose in majority of studies (table 2), possibly because at higher doses, there are increased chances of direct activation of non-target immune cells such as macrophages and innate immune cells through cell–cell interactions before and/or as CAR-T cells interact with their target tumor cells. Interestingly, the onset of CRS was within 7 days in most studies and the time to reach peak expansion was 2 weeks in most studies (online supplemental table S5) supporting the hypothesis that the initiation of CRS was possibly related to CAR-T cell activity before reaching Cmax.

Tumor burden is another factor that is commonly considered during CAR-T cell treatment and its association with response is debated during the clinical development of CAR-T cells. In response to the question of whether tumor burden is directly or inversely associated with response, the results show that high tumor burden is very likely to be associated with low disease response and with high adverse events. All the studies identified in the review showed an inverse association between tumor burden and disease response (online supplemental table S6) except the study by Wang *et al*[80] which, unlike all other studies, used a comparatively different cut-off (</≥ cohort median) and observed that patients with tumor burden less than median had lower ORR. Intriguingly,

peak CAR-T cell expansion (Cmax), a parameter shown to be associated with response was found to be lower in patients with high tumor burden.[90] The findings are in line with previous studies that noted that high tumor burden was associated with lower response to immunotherapy. In fact, some of the CAR-T cell studies have even proposed the tumor burden-based risk-adoptive dosing approach[46 53] or aggressive treatment with chemotherapy or radiotherapy to shrink the tumors[91] prior to CAR-T cell treatment.

The review was mainly able to achieve the difficult task of consolidating the learnings from different types of CAR-T cell studies performed in heterogenous patient population by evaluating the association between dose and response separately for each study. The findings from our study show that the answer to the question of whether there is a dose–response correlation is possibly not a simple yes or no. Our study identified and listed the trials that saw increased response at higher dose levels and the trials that had similar response at all dose levels and described the common factors seen in both categories. The studies that did not see any association between dose and response either had a very low response rate at all the doses tested indicating that the cell product was not effective or had a very high response rate at all the doses tested indicating that the product was very effective and lowest dose administered was able to achieve maximum possible response. Similarly, in the studies that saw an increase in response with dose increments, lowest dose was apparently not sufficient to achieve optimal effector to target cell ratio (E-T ratio) and drive the response. The findings support the point that CAR-T cell therapy is a living drug that involves in vivo proliferation of cells and in vivo expansion of CAR-T cells is possibly more relevant than the starting dose and also support the point that the effector to target cell ratio (E-T ratio) needs to be considered during determination of the dose as low E-T ratio can result in ineffective response. Finally, the summary of median time to peak expansion, onset of response, onset of CRS and onset of neurotoxicity included in the review support the hypothesis that PKs of CAR-T cells and mechanisms are comparable across all hematological cancers.

Based on the mechanisms of CAR-T cell activity and the results from the studies included in the review, a sigmoidal dose response curve (figure 4) can be proposed. It includes a threshold dose defined as dose needed to achieve the least effective E-T ratio and the optimal efficacy dose, defined as lowest dose that had most effective E-T ratio and highest efficacy was comparable across majority of the studies irrespective of target antigen and intracellular signaling domain. A positive correlation between dose and ORR is less likely above the optimal efficacy dose, and further increase in dose would likely increase the toxicity of CAR-T cells (figure 4).

Limitations

Review is limited by the studies included. All studies were non-randomized, open label, lacked control cohort and the majority had small sample size. Furthermore, majority of the studies did not include independent review committee for selection of subjects (selection bias) and had >20% loss of subjects to follow-up (attrition bias; online supplemental table S2). Studies also did not report granular differences in CAR-T cell expansion, onset of response and persistence between dose levels. Durability of response and its correlation with dose was also not explored within the studies. Finally, the review excluded solid tumors and studies in children, which could limit the application of the findings to adult hematological cancers.

CONCLUSION

In summary, the findings from the systematic literature review suggest that there may be an optimal dose of efficacy in CAR-T cell therapeutics at which maximal clinical effect is achieved and beyond which no additional antitumor effect can be observed. However, increasing the dose beyond the optimal efficacy or increasing the dose when the ORR is relatively high may result in higher incidence and/or severity of adverse events. The findings also show that high tumor burden is likely associated with lower response to CAR-T cell treatment.

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