Cytotherapy, 2019; 00: 1–13

International Society
ISCT
Cell & Gene Therapy

The efficacy of anti-CD19 chimeric antigen receptor T cells for B-cell malignancies

JUN-XIA CAO, WEI-JIAN GAO, JIA YOU, LI-HUA WU, JIN-LONG LIU & ZHENG-XU WANG

Biotherapy Center, The Seventh Medical Center of PLA General Hospital, Beijing, China

Abstract

Immunotherapy with chimeric antigen receptor T (CAR-T) cells has proved remarkably effective in recently published clinical trials. In this meta-analysis, we performed a systematic review in terms of the clinical response treated with CAR-T cells in acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL) and lymphomas patients. Thirty-eight published clinical studies including 665 patients were eligible for response rate (RR) evaluation. The overall pooled RR of CD19-CAR-T cells was 72% (95% confidence interval: 62–77%). The various clinical parameters were analyzed. RR was 81% in ALL, 68% in lymphoma and 70% in CLL. RR in patients who received interleukin (IL)-2 was 70%, whereas in those who did not receive IL-2, it was 74%. RR was 75% with lymphodepletion and 56% without lymphodepletion. RR with autologous cells was 76% and 57% with allogeneic cells. In conclusion, this meta-analysis showed a high clinical RR of CD19-CAR-T cell–based immunotherapy in patients with refractory B-cell malignancies.

Key Words: *CAR-T, acute lymphocytic leukemia, chronic lymphocytic leukemia, lymphomas, meta-analysis*

Introduction

The adoptive transfer of T cells engineered to express artificial chimeric antigen receptors (CARs) that target a tumor cell surface molecule has emerged as an exciting new approach for cancer immunotherapy, with successful reports first published in 2011, showing the remarkable efficacy of CAR-T cells in treating hematological malignancies [1]. Clinical trials in patients with advanced B-cell malignancies treated with CD19-specific CAR-T cells have shown impressive antitumor efficacy [2]. The target CD19, which has expression limited to mature B cells rather than other hematopoietic cells or non-hematopoietic tissues, is the most well-studied and successful CAR [3,4]. In first generation CARs, the T-cell signaling domain comprised an intracellular portion of the CD3ζ subunit. By contrast, the second and later generations of CARs incorporate two types of T-cell signalling domains: co-stimulatory domains and a T cell activation domain, derived from CD28 (CD28/CD3ζ or 28z) or 4-1BB (4-1BB/CD3ζ or BBz) [5]. It was demonstrated anti-CD19 CAR-T cells become a new standard of care for patients with chemotherapy-refractory ALL and lymphoma.

The first two CAR-T-cell products, Yescarta from Kite Pharma/Gilead and Kymriah from Novartis, were approved by the U.S. Food and Drug Administration (FDA) in 2017, with prominent efficacy results [5–7]. The FDA approved tisagenlecleucel (named KYMRIAH, CTL019) with CD28/CD3ζ on August 30, 2017. On the basis of clinical studies, 75 patients received an infusion of tisagenlecleucel, and the overall remission rate within 3 months was 81% [5,6]. The FDA then authorized axicabtagene ciloleucel (Yescarta, KTE-C19) with 4-1BB/CD3ζ on October 18, 2017. In this multicenter, phase 2 trial, Neelapu SS and colleagues enrolled 111 patients with large B-cell lymphoma. Eighty-three (82%) of 101 patients included in the intention-to-treat analyses had an objective response, with 55 (54%) patients achieving a complete response (CR) and 28 (28%) patients a partial response (PR) [5,7]. The CD19 CAR-T product JCAR017 from Celgene (originally developed by Juno) is also in the advanced development phase, and the first clinical results from the TRANSCEND NHL 001 were presented in 2017, with 91 patients treated and evaluable for safety and 88 for efficacy [8].

Correspondence: **Zheng-Xu Wang**, PhD, Biotherapy Center, The Seventh Medical Center of PLA General Hospital, No. 5 Nan Men Cang Rd, Dongcheng District, Beijing, 100700, China. E-mails: zhxuwang@qq.com, zhxwang18@hotmail.com

(Received 12 December 2018; accepted 9 April 2019)

https://doi.org/10.1016/j.jcyt.2019.04.005

Thus far, more than 10 meta-analyses have been published to evaluate the efficacy and the safety of CD19 CAR-T immunotherapy. Early in 2013, 29 patients were enrolled in a systematic review of phase I clinical trials, the 6-month progression free survival (PFS) for this cohort was 50.0 ± 9.9% [9]. Next, six trials involving 50 patients were analyzed in another systematic review in 2015 [10]. The results demonstrated that the overall response rate (RR) was 48% (CR 24%), and 6-month and 1-year PFS were 43% and 27%, respectively. Soon after, 14 clinical trials including 119 patients were eligible for evaluation [11]. In this analysis, the overall pooled RR of CD19-CAR-T cells was 73% and 93% in ALL patients and 36% in lymphoma patients. In 2017, a systematic review and meta-analysis including anti-CD19 and anti-CD20 CAR-modified T cells were involved in 16 studies with 195 patients [12]. The pooled analysis showed an overall RR of 61%. In another meta-analysis, 19 published clinical studies with total of 391 patients were included [13]. The pooled rate of complete remission (CRe) was 55%, and the pooled rate of partial remission (PRe) was 25%. In 2018, the incidence of severe cytokine release syndrome was analyzed in 19 clinical trials included 313 patients [14]. The pooled severe cytokine release syndrome proportion was 29.3% in B-cell (B-)ALL, 38.8% in B-CLL and 19.8% in B-NHL. As noted, although the clinical benefit varies greatly among trials, the overall efficacy of CAR-T cell is significant, leading to optimism that this approach will be useful in treating tumors.

Some key questions remain regarding the efficacy and safety, including the design of CARs and efficiency of gene transfer, the persistence of CAR-T cells and their cytotoxicity, the optimization of preconditioning and cytokine supplement, and the mitigation of toxicity. Furthermore, along with the drug approval, larger clinical trials are gradually expanding, and data are increasing [15,16]. To attempt to answer these questions, we performed a meta-analysis to systematically evaluate the outcomes of 38 completed CD19-targeted CAR-T clinical trials including 665 patients, which represents the largest number of patients CAR-T meta-analysis to date.

Methods

Literature search and inclusion and exclusion criteria

The trials analyzed in the present study were identified through an electronic search of the PubMed database, the Cochrane Central Registry of Controlled Trials and ClinicalTrials.gov. The search strategy included the medical subject headings "chimeric antigen receptor" and "CD19," as well as free text searches. We also searched the reference lists of published trials and the relevant review articles. Two authors identified articles eligible for further review by screening titles and abstracts. When a study was considered relevant, the article was reviewed thoroughly. In addition, bibliographic references of identified articles were reviewed to find articles of interest not indexed by the electronic research.

No language limitations were imposed. The initial search was performed in November 2013 and was updated in August 2018. Manual searches were based on the reference lists and conference proceedings of the American Society of Clinical Oncology Annual Meetings and the European Cancer Conference. We excluded abstracts that were never subsequently published as full papers and studies performed on animals and cell lines.

Study selection and data extraction

The list of references of each eligible article was manually evaluated for relevance to the review topic. The selected publications were independently assessed by two authors, and any discrepancies in the interpretation of the findings were discussed and resolved by consensus of both the authors.

We collected information including authors' names, journal and year of publication, sample size per arm, regimen used, median or mean age of the patients, culture of cells, origin type, dosage and clinical response for all of the trials in the present study. Two authors independently screened the data.

Definition of outcome measures

The primary outcomes were CR/PR and CRe/PRe. Patients with response to CAR-T cells immunotherapy were divided to two groups: positive response group (patients achieved CR and PR), and negative response group, which patients achieved stable disease and progress disease. The RR was calculated as the percentage of all patients (positive and negative combined) achieving a CR or PR.

Statistical analysis

We performed a meta-analysis using Comprehensive Meta-analysis 2.0. Weighted hazard ratio (HR) with 95% confidence intervals (CIs) was calculated for each outcome. Pooled RR were calculated using fixed- and random-effects models depending on the heterogeneity across the included studies. The heterogeneity was assessed using I^2 values. Generally, I^2 values of 25% represent low heterogeneity, and I^2 values of 50% and 75% are evidence of moderate and high heterogeneity, respectively. When no statistically significant heterogeneity existed, the analysis was calculated with a fixed-effect model; otherwise, a random-effects model was used. P values <0.05 were considered statistically significant. We performed subgroup analysis to assess the

efficacy of CD19 CAR-T-cells with different clinical parameters in ALL, CLL and lymphoma patients. SPSS 11.5 and OpenEpi online software were also used to carry out the data analysis.

Results

Selection of the clinical trials

The electronic search yielded 623 references. After a title and abstract review, 564 publications were excluded for various reasons (258 review articles, 251 *in vitro* experiments, 18 animal models, 37 other studies including systematic review, case reports, comparative studies, editorials). A total of 59 clinical trials were selected as potentially relevant, and their full texts were retrieved for a more detailed assessment. We subsequently excluded 21 of these 59 studies for not providing detailed patient clinical data or details on the therapeutic response. The procedure used to select the clinical trials is shown in Figure 1. Thus, 38 articles reporting clinical trials of CD19 CAR-T immunotherapy were further selected (Table 1). All of the studies were published in English and comprised 665 patients [17–54].

Characteristics of CAR-T cell therapy

After selection, 38 eligible trials with a total of 665 (56.4% male; 43.6% female) patients were included in the present analysis [17–54]. The tumor included were ALL, CLL and B-cell lymphoma. The clinical data for the trials are shown in Table 1. The mean age of the included patients was 43.6 years according to the available data from 8.5 to 68.7. The included trials consisted of patient with the following malignancies: 325 (50.3%) ALL, 53 (8.2%) CLL, 268 (41.5%) lymphomas including DLBCL, MCL, FL, SMZL, PMBCL and TFL (Table 1). The viral vector of CAR was lentiviral in 20 clinical trials and retroviral in 17 studies; only one clinical trial used nonviral sleeping beauty transposon in the 38 included trials [33]. In addition, one publication evaluating two product manufacturing processes reported no patients with CR (listed on Table 1, but not included in the data analysis) [24].

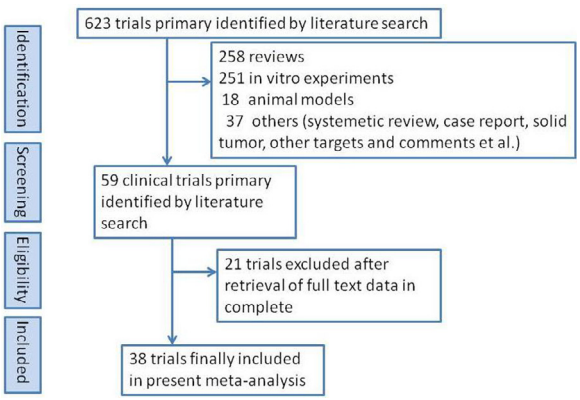


Figure 1. Flow diagram showing the record identification, screening and study inclusion processes.

We defined the outcome endpoints of CR and PR according to the original record in the included clinical trials. Eleven clinical trials reported CR and PR [28,30,35,36,39,42,43,45,51,52,54], in addition another 27 clinical trials reported CRe and PRe [17–29,31,32–34,37,38,40,41,44,46–50,53]. In two clinical trials, only remission was reported [17,22], and we calculated them as CRe and PRe. Complete remission with incomplete count recovery, molecular complete remission, continuous complete remission, second complete remission, minimal residual disease remission and bone marrow remission were also reported in the clinical trials [27,33,38,46], thus we combined them for our analysis. We demonstrate the primary outcomes of stable disease and progressive disease of the included clinical trials in Table 1. Some studies did not report stable or progressive disease, and others reported patients who died in remission, died of disease, were alive with disease, or had no detectable leukemia in the cerebrospinal fluid. Still other studies had no information available or remission/response were not reported or were not performed or evaluable. These are shown in the response categories of Table 1.

Meta-analysis of RR of CD19-CAR-T cell in patients with refractory B-cell malignancies

In this analysis, CR and PR were added as RR of patients to evaluate the efficacy of the CAR-T cell therapy. For all of the 665 included patients of 35 clinical trials in this analysis [17–54], RR of 72% (473/659) was observed with HR of 0.70 (95% CI: 0.62–0.77, $P = 0.000$) in patients of B-cell malignancies treated with CAR-T cells [17–54]. There was significant heterogeneity among the studies, with an I^2 of 66, Q = 98 (Figure 2). The random-effects model was applied. Previous reports have included 14 clinical trials with 131 patients who were also recruited in our analysis [17–30] with results similar to ours [11].

RR in patients with different diseases

To confirm the results of the meta-regression, subgroup analysis was performed. First, we compared the clinical responses among malignancies type (ALL, CLL and lymphoma). For ALL, RR of 81% (223/277) was observed, with an HR of 0.80 (95% CI: 0.68–0.88, $P = 0.000$) in 14 clinical trials [25-29,32,35,38,41,46,48,50,52,53]. There was significant heterogeneity among the studies with an I^2 of 64, Q = 36 (Figure 3). For lymphoma, RR of 68%

Table 1. Clinical information from the eligible trials for the meta-analysis.

Trial reference	Tumor characteristic	No. pts	Age	Sex F (M)	T-cell tx	LD	Origin	Total cells injected ($\times 10^9$)	CAR construct/viral	Study center	Response
Jensen 2010 [17]	Lymphoma	4			IL-2	Yes	Auto	1×10^8–2×10^9 cells/m^2	CD4-CD3z/retro	CH	2 R, 1 DOD, 1 P
Kochenderfer 2015 [18]	CLL(4) + lymphoma	15	51.7	8 (7)	IL-2	Yes	Auto	$(1–5) \times 10^6$/kg	CD28-CD3z/retro	NIH	8 CR, 4 PR 1 SD, 2 NA
Kochenderfer 2010 [19]	Stage IVb FL	1	X + 6	1	IL-2	LK	Auto	4×10^8	MSGV-FMC63-28Z/retro	NCI	1 PR
Kochenderfer 2013 [20]	CLL (4) + DLBCL (2) + MCL (4)	10	52.4	8 (2)	IL-2	No	Allo	$(1–10) \times 10^6$/kg	scFv-CD28-CD3/retro	NCI	2 PR 6 SD, 2 PD
Kochenderfer 2012 [21]	CLL (4) + FL (3) + SMZL (1)	8	55.8		IL-2	LK	Auto	$(0.3–3) \times 10^7$/kg	(MSGV)–FMC63-28Z/retro	NCI	1 CR, 5 PR 1 SD
Brentjens 2011 [22]	ALL (2) + CLL (8)	10	63.9	8 (2)	IL-2	LK	Auto	1.8×10^8–3.2×10^9/kg	19-28z/retro	MSKCC	1 R, 3 NR, 1 NE, 3 SD, 1 PD
Kalos 2011 [23]	CLL	3	68.7	3	No IL-2	Yes	Auto	1.4×10^7–1.1×10^9 (cells/kg)	CD137 (4-1BB)- CD3-zeta/lenti	ACC	2 CR, 1 PR
Savoldo 2011 [24]	NHL+DLBCL	6	53.3	5(1)	IL-2	No	Auto		CD19-28ζ/retro	Center for Cell and Gene Therapy	0 CR 2 SD, 4 PD
Brentjens 2013 [25]	ALL	5	52.4	4(1)	No IL-2	LK	Auto	$1.5–3 \times 10^6$	CD28/CD3ζ/ retro	MSKCC	5 CR
Grupp 2013 [26]	ALL	2	8.5	(2)	No IL-2	Yes	Auto	1.4×10^6–1.2×10^7	CTL019/lenti	CHP	2 CR
Davila 2014 [27]	ALL	16	50	12 (4)	No IL-2	LK	Allo	3×10^6	19-28z/retro	MSKCC	14 CR (88%), 2 NR
Lee 2014 [28]	ALL	21	14.7	14 (7)	No IL-2	LK	Auto	4×10^6	MSGV-FMC63-28Z/retro	Pediatric Oncology Branch	14 CR (88%), 3 SD, 4 PD
Maude 2014 [29]	ALL	30	29	18(12)	No IL-2	Yes	Auto	0.76×10^6–20.6×10^6	CTL019/lenti	CHP	27 CR (90%)
Cruz 2013 [30]	ALL (4) + CLL (4)	8	38.5	5 (3)	IL-2	No	Allo	1.9×10^7 (2 infusions)–1×10^8 (1 infusion)	CD19.CAR-VST/retro	Baylor College of Medicine	3 CR; 1 PR 3 PD; 1 SD
Porter 2011 [31]	Stage I CLL	1	X + 13	1	No IL-2	Yes	Auto	1.5×10^5	CD137 (4-1BB)-CD3-zeta/lenti	ACC	1 CR
Gardner 2016 [32]	ALL	7	26.5	(2)	No IL-2	Yes	Auto	2×10^6–1×10^7	FMC63 CD19-CD28-4-1BB and CD3z/lenti	SCRI	7 CR
Partow Kebriaei 2016 [33]	ALL (17) + Nodular HL (1) + FL (3) + DLBL (4) + MCL (1)	26	40		IL-2	No	Auto (n = 7) or Allo (n = 19)	$10^6 - 5 \times 10^9$	CD19RCD28/SB transposon (nonviral)	MDACC	16 CR, 2 DIR, 5 DOD, 3 AWD
Brudno 2016 [34]	ALL (5) + CLL (5) + DLBCL (5) + MCL (5)	20	48.1	11 (9)	No IL-2	No	Allo	0.4×10^6–7.8×10^6	CD28-CD3z/retro	NIH	6 CR, 2 PR 8 SD; 4 PD
	ALL	9	38.9	4 (5)	IL-2	Yes					

(continued on next page)

Table 1. (***Continued***)

Trial reference	Tumor characteristic	No. pts	Age	Sex F (M)	T-cell tx	LD	Origin	Total cells injected ($\times 10^9$)	CAR construct/viral	Study center	Response
Dai 2015 [35]							Auto or donor-derived	7.9×10^8(1.0 $\times 10^7$/kg)-2.2 $\times 10^8$(3.0 $\times 10^6$/kg)	(HM852952.1) CD19 4-1BB and CD3z/lenti	Chinese PLA General Hospital	2 CR, 2 MRD, 3 PD, 1 CNS1
Garfall 2015 [36]	(lymphoma) MM	1	48	(1)	No IL-2	No	Auto	1×10^7-5×10^7	CTL019/lenti	ACC	1 CR
Joseph A. Fraietta 2016 [37]	CLL	3	62	3	IL-2	No	Donor		CTL019 (4-1BB and CD3z) /lenti	UP	1 CR, 2 PR
Cameron J. Turtle 2016 [38]	ALL	29	40		IL-2	Yes	Auto	CD4: 1×10^5- 1.16×10^7 CD8: 3×10^4-1×10^7	FMC63 CD19-CD28-4-1BB and CD3z/lenti	FHCRC	27 BM remission (93%)
Bhoj 2016 [39]	ALL (13)+ CLL (2) + FL (1)	12	25		IL-2	Yes			CTL019/lenti	UP	12 CR
Porter 2015 [40]	CLL	14	66.9	12 (2)	IL-2	Yes	Auto	0.14×10^8-11×10^8	CTL019/lenti		4 CR, 4 PR, 6 NR
Hu 2016 [41]	R/R ALL	15	<60		IL-2	Yes	Auto	$1.1-9.8 \times 10^6$ CAR-T cells/kg	FMC63 CD19-4-1BB/ CD3ζ/lentiviral	Zhejiang University China	12 CR, 1 NE, 1 SD, 1 PD
Turtle 2016 [42]	Non-Hodgkin lymphoma	32	57	27 (32)	IL-2	Yes	Auto	$2 \times 10^7-8.8 \times 10^6$ CAR-T cells/kg	FMC63 CD19-CD28-4-1BB-CD3ζ/lenti	FHCRC	11 CR
Wang 2016 [43]	B-cell NHL DLBCL + MCL	16	59.6		No IL-2	Yes	Auto	$25-200 \times 10^6$ CAR-T_{CM} cells	FMC63 CD19-CD3ζ/ CD28/lenti	SCRI	13 CR, 2 PR, 1 PD
Kochenderfer 2017 [44]	DLBCL + MBCL + MCL	22	53		IL-2	Yes	Auto	$1-6 \times 10^6$ CAR-T cells/kg	CD3ζ/CD28/retro	NCI	12 CR, 4 PR 2 SD, 4 PD
Locke 2017 [45]	DLBCL (I–IV)	7	52.3	5(2)	IL-2	Yes	Auto	2×10^6 CAR-T cells/kg	CD3ζ/CD28(KTE-C19)/retro	Moffitt Cancer Center	4 CR; 1 PR 1 SD 1 NE
Y. Chen 2017 [46]	B-ALL	6	26.5	1(5)		Yes	Donor	1.7×10^8 cells/kg	4S CAR-T 19/lenti	Peking University	5 MRD remission
Z. Cheng 2018 [47]	B-cell leukemia (ALL + CLL)	7	28.3	4(3)	IL-2	Yes	Auto	1×10^6 CAR-T cells/kg	28ζ/BBζ/retro	Henan University	5 CR, 2 PD
Cao 2018 [48]	R/R ALL	18	20.3			Yes	Auto	1×10^6 humanized CD19 CAR-T cells/kg	4-1BB/ CD3ζ/lenti	Xuzhou Medical University	13 CR, 2 NA, 3 NR
Schuster 2017 [49]	Lymphoma	28	58.5	18 (10)		Yes	Auto	Total 1.00×10^8 to 5.00×10^8 CTL019 5.79×10^6 cells/kg	CTL019/lent	UP	16 CR
Park 2018 [50]	ALL	53	44			Yes	Auto	0.8×10^3/mm^3	CD3ζ/CD28/retroviral	MSKCC	44 CR
Neelapu 2017 [51]	Lymphoma	111	57.5	68 (43)	IL-2	Yes	Auto	2×10^6 CAR-T cells/kg (ZUMA-1, phase 2)	axicabtagene ciloleucel (axi-cel) /KTE-C19/Yescarta (CD28)/retro	MDACC	57 CR, 28 PR, 11 SD

(*continued on next page*)

Table 1. (*Continued*)

Trial reference	Tumor characteristic	No. pts	Age	Sex F (M)	T-cell tx	LD	Origin	Total cells injected ($\times 10^9$)	CAR construct/viral	Study center	Response
Wei 2018 [52]	ALL	23	35.8	10(13)			Donor	3.0×10^7 to 10.0×10^7/kg	4-1BB/ CD3ζ/lenti	Zhejiang University	8 CR, 3 PR, 12 SD+PD
Gardner 2017 [53]	ALL	43	12.2	23(22)	IL-2	Yes	Auto	$0.5-1 \times 10^6$ CAR-T cells/kg	CD3ζ/CD28/lenti	SCRI	40 CR
Turtle 2017 [54]	CLL	24	59.5		IL-2	Yes	Auto	2×10^5, 2×10^6 or 2×10^7 CAR-T cells/kg	CD3ζ/4-1BB/ CD28/lenti	FHCRC	4 CR, 13 PR 5 PD, 1 SD, 1 ND

The table summarizes the basic information including disease type, number of patients, patient age and details of the immunotherapy including the cell type, CAR construct, dosage and response. ACC, Abramson Cancer Center; Allo, allogeneic; Auto, autologous; AWD, alive with disease; BM, bone marrow; CH = City of Hope National Medical Center; CHP = Children's Hospital of Philadelphia; CNS1, no detectable leukemia in the cerebrospinal fluid; CR, complete response or complete remission; DIR, died in remission; DLBCL, diffuse large B-cell lymphoma; DOD, died of disease; FHCRC, Fred Hutchinson Cancer Research Center; FL, follicular lymphoma; LD, lymphodepletion; lenti, lentiviral; LK, leukapheresis; M, male; MCL, mantle cell lymphoma; MDACC MD Anderson Cancer Center; MM, multiple myeloma; MRD, minimal residual disease; MSKCC, Memorial Sloan-Kettering Cancer Center; NA, not available; NCI, National Cancer Institute; ND, not done; NE, not evaluable; NIH, National Institutes of Health; NR, no remission or no response; P, progression; PD, progressive disease; PMBCL, primary mediastinal (thymic) large B-cell lymphoma; PR, partial response or partial remission; R, remission; retro, retroviral; R/R, relapsed/refractory; SB, sleeping beauty; SCRI = Seattle Children's Research Institute; SD, stable disease; SMZL, splenic marginal zone lymphoma; TFL, transformed follicular lymphoma; tx, treatment; UP, University of Pennsylvania.

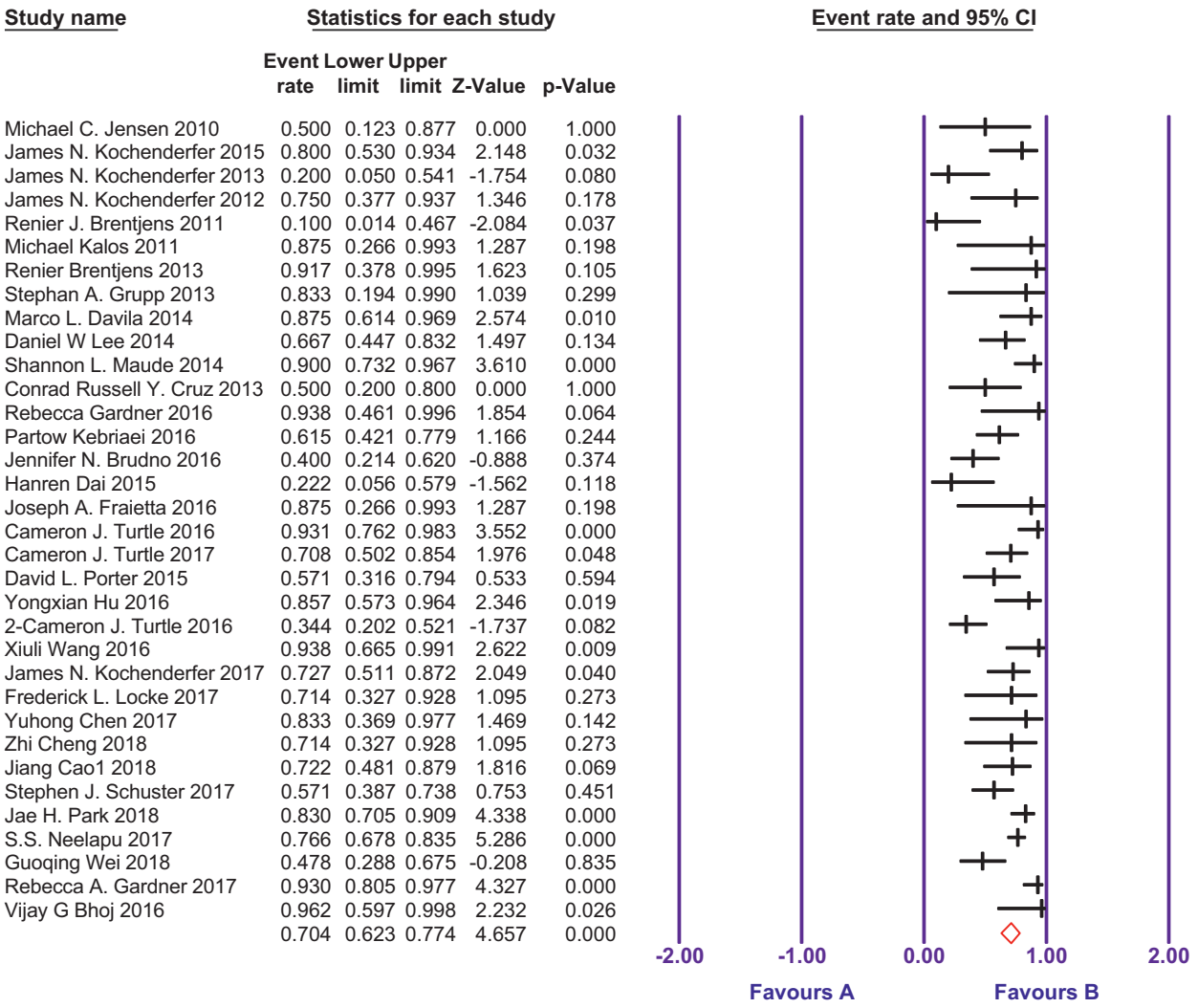
(130/192) was observed, with an HR of 0.64 (95% CI: 0.40−0.82, $P = 0.000$) in five clinical trials [7,17,42,43,49]. There was significant heterogeneity among studies with an I^2 of 83, Q = 23 (Figure 3). For CLL, RR of 70% (31/44) was observed, with an HR of 0.68 (95% CI: 0.53−0.80, p = 0.02) in four clinical trials [23,37,40,54]. There was no significant heterogeneity among the studies with an I^2 of 0.000, Q = 2 (Figure 3). The random-effects model was applied. Thus, ALL patients had higher response rate (81%) than CLL patients (70%) and lymphoma patients (68%) (Figure 3).

Meta-analysis of RR in patients with different clinical parameters

Then meta-regression analysis was performed based on CAR-T cell protocols including T-cell origin, interleukin (IL)-2 administration and lymphodepletion before T-cell infusion. For autologous CAR-T cell therapy, RR of 76% (391/515) was observed, with an HR of 0.75 (95% CI: 0.67−0.82, $P = 0.000$) in 26 clinical trials [17−19,21−26,28,29,32,38−41,43,45,47−51,53,54]. There was significant heterogeneity among the studies, with an I^2 of 62, Q = 63 (Figure 4). For allogeneic CAR-T cell therapy, RR of 57% (64/110) was observed with HR of 0.56 (95% CI: 0.36−0.74, $P = 0.543$) in seven clinical trials [20,27,30,34,37,46,52]. There was significant heterogeneity among the studies, with an I^2 of 58, Q = 14 (Figure 4). The random-effects model was applied. Patients who received an autologous regimen had a higher response rate (76%) than patients with an allogeneic regimen (57%), which was significant difference ($P < 0.05$) by chi-square test.

A forest plot analysis was conducted for RR and CIs in patients receiving IL-2 versus no IL-2. For CAR-T cell therapy with IL-2, RR of 70% (287/410) was observed, with an HR of 0.66 (95% CI: 0.55−0.76, $P = 0.006$) in 21 clinical trials [17,18,20−22,24,30,33,35,37−42,44,45,47,51,53,54]. There was significant heterogeneity among the studies, with an I^2 of 70, Q = 64 (Figure 5). For CAR-T cell therapy with no IL-2, RR of 74% (186/250) was observed, with an HR of 0.75 (95% CI: 0.63−0.84, $P = 0.000$) in 14 clinical trials [23,25−29,32,34,43,46,48−50,52]. There was significant heterogeneity among the studies, with an I^2 of 60, Q = 33 (Figure 5). The random-effects model was applied. Patients who did not receive IL-2 had a higher response rate (74%) than those who received IL-2 (70%), but no significant difference was seen by chi-square test ($P > 0.05$).

Forest plots for RR and CIs in patients who underwent or did not undergo lymphodepletion were performed. For CAR-T cell therapy with lymphodepletion, RR of 75% (412/547) was observed, with an HR of 0.75 (95% CI: 0.66−0.82, $P = 0.000$) in 27 clinical



Meta Analysis

Figure 2. Forest plot of RR of CD19-CAR-T cells in patients with refractory B-cell malignancies. A random effects meta-analysis model was used. Each trial is represented as a square, and the odds ratio for each trial is shown in the center. The size of the square is proportional to the information in each trial. The ends of the horizontal bars denote 95% CI. The red diamond shows the overall odds ratio for the combined results of all trials.

trials [17,18,21–29,32,35,38–43,45–51,53,54]. There was significant heterogeneity among studies, with an I^2 of 64, Q = 73 (Figure 6). For CAR-T cell therapy without lymphodepletion, RR of 56% (50/90) was observed, with an HR of 0.54 (95% CI: 0.37–0.70, $P = 0.674$) in seven clinical trials [20,24,30,33,34,37,44]. There was significant heterogeneity among the studies with I^2 of 51, Q = 10 (Figure 6). Patients who underwent a lymphodepletion regimen had a higher response rate (75%) than patients who did not (56%), a significant difference ($P < 0.05$) by chi-square test.

We checked the viral vector for CAR construct and its impact on outcome by chi-square test. Lentiviral vector included 316 (233) patients in 20 clinical trials [23,26,29,31,32,35–43,46,48,49,52–54], and retroviral vector comprised 324 (229) patients in 17 clinical trials [17–22,24,25,27,28,30,34,44, 45,47,50,51]; there was no significant difference with regard to the effect on CAR-T therapy ($P > 0.05$) by SPSS software. In addition, the costimulatory domain, which included CD28 with 364 (268) patients in 16 clinical trials [18–22,24,25,27,28,34,43–45,50,51,53] and 4-1BB with 159 (123) patients in 14 clinical trials [23,26,29,31,35–37,39–41,47–49,52], revealed no association with the effect of CAR-T therapy ($P > 0.05$).

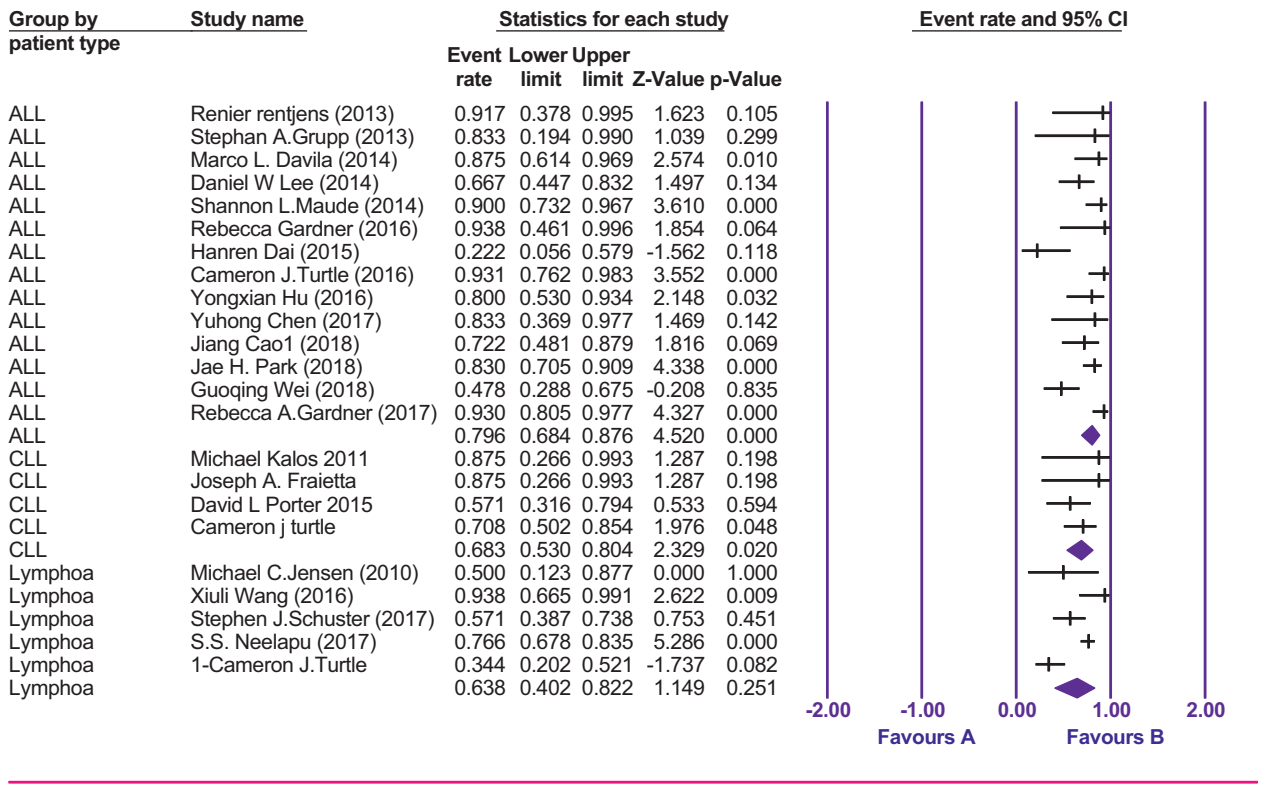


Figure 3. Comparison of RR in patients with different diseases. A random effects meta-analysis model was used in the analysis.

Discussion

CD19-CAR-expressing T cells have evidenced remarkable activity against B-cell malignancies, especially CLL, indolent NHL and ALL, with significant responses seen even in chemo-refractory disease, and more generalizations have emerged. In this report, a meta-analysis of the most up-to-date clinical data was carried out to evaluate the efficacy of CAR-T therapy in the treatment of ALL, CLL and lymphoma. The overall pooled RR (CR+PR) of CD19-CAR-T cells was 72% (95% CI: 62−77%), which is in agreement with previously published meta-analyses. In one analysis, the pooled CR rate was 55% and PR was 25% [13], whereas another analysis showed an overall response rate of 61% with CR of 42% and PR of 19% [12], and an overall pooled RR of 48% was reported in one study [10]. Thus, most analysis demonstrated that CAR-T therapy is effective in B-cell malignancies, and our analysis also elucidated associations between clinical response and clinical parameters that have not been previously examined in other meta-analysis.

The different diseases type, lymphodepletion, IL-2 administration and the origin of CAR-T cells were separately analyzed as impact factors associated with the clinical response. RR was 80% for ALL, 68% for lymphoma and 70% for CLL. In a previous report, ALL patients had a higher response rate (93%) than CLL patients (62%) and lymphoma patients (36%), and this included 14 clinical trials that were also part of our analysis [11]. Thus, our analysis obtained similar results as previous studies, and it was known that the clinical data of CTL019 were based on an 81% overall remission rate and KTE-C19 was 82% CR +PR [6,7]. In general, the overall efficacy to date is approximately 80% in the reported clinical trials.

In our analysis, the RR in the patients who received IL-2 was 70%, whereas that for patients who did not receive IL-2 was 74%; thus, there was no significant difference by chi-square test ($P > 0.05$). Serum IL-2 levels (85% vs. 31%, $P = 0.04$) were positively associated with patients' response to CAR-T cells [55]. It should be noted that we did not consider IL-2 administration to cells or patients, which have been subgroup analyzed as prognostic factors for RR in other reports, with no significant difference [55]. In our meta-analysis, we collectively referred to them as with or without IL-2, which would introduce bias into the analysis.

RR was 75% with and 56% without lymphodepletion in our analysis, which was similar to other

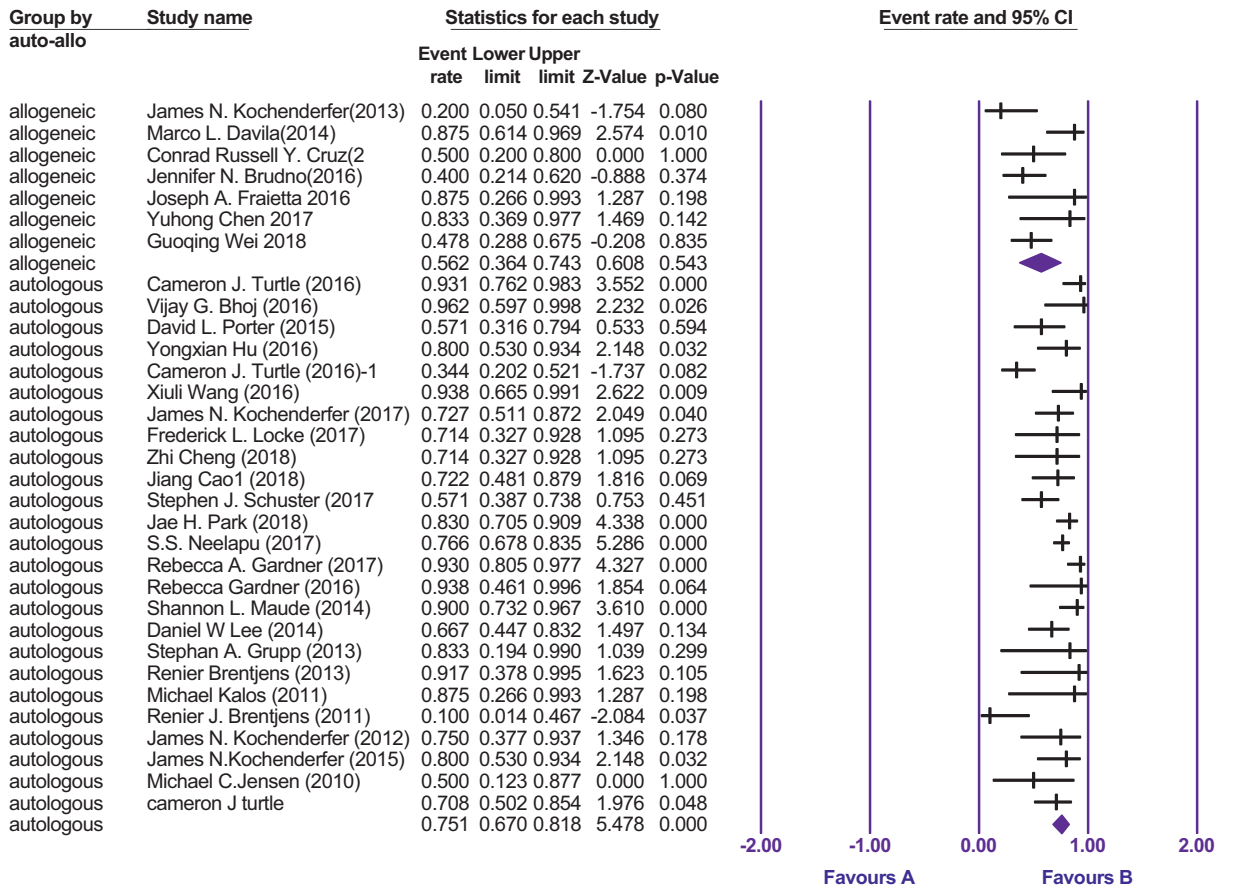


Figure 4. Comparison of RR in patients with the CAR-T cell origin (autologous or allogeneic). The random effects meta-analysis model was used in the present analysis.

reports (72% vs. 44%, $P = 0.0405$) [55]. In our analysis, treatment with or without lymphodepletion showed a significant difference by chi-square test ($P < 0.05$). Extensive evidence from mouse studies indicates that lymphocyte depletion in the recipient enhances activity of the adoptively transferred T cells by causing increased serum levels of cytokines such as IL-15 and possibly by depleting regulatory T-cell numbers [56,57]. Despite some exceptions, it has demonstrated lymphodepletion before CAR-T cell administration may be an important component of this treatment approach [55]. In our analysis, RR with autologous cells was 76% and with allogeneic cells was 57% ($P < 0.05$). There was a significant difference in efficacy with autologous versus allogeneic cells in our analysis; other studies have also reported side effects between donor-derived CAR-T cell versus autologous CAR-T cells [58]. In a future study, we will specifically address questions about such adverse effects.

Given the differences in the integrated costimulatory domain, the optimal method for CAR transfer into T cells (retroviral, lentiviral, or other), bias could occur and affect the association assessment. We analyzed the viral vector for CAR construct and the impact of that on the outcome by chi-square test and found that lentiviral and retroviral vectors did not demonstrate a significant difference in the effect of CAR-T therapy ($P > 0.05$). The costimulatory domain including CD28 and 4-1BB also revealed no association with the effect of CAR-T therapy ($P > 0.05$), which was similar to the results of a prior publication [14].

Limitations

This meta-analysis can help strengthen the case for the expansion of CAR-T therapy, but before drawing inferences from the studies included herein, caution is required because of the variability in the biology of various malignancies that were treated in included

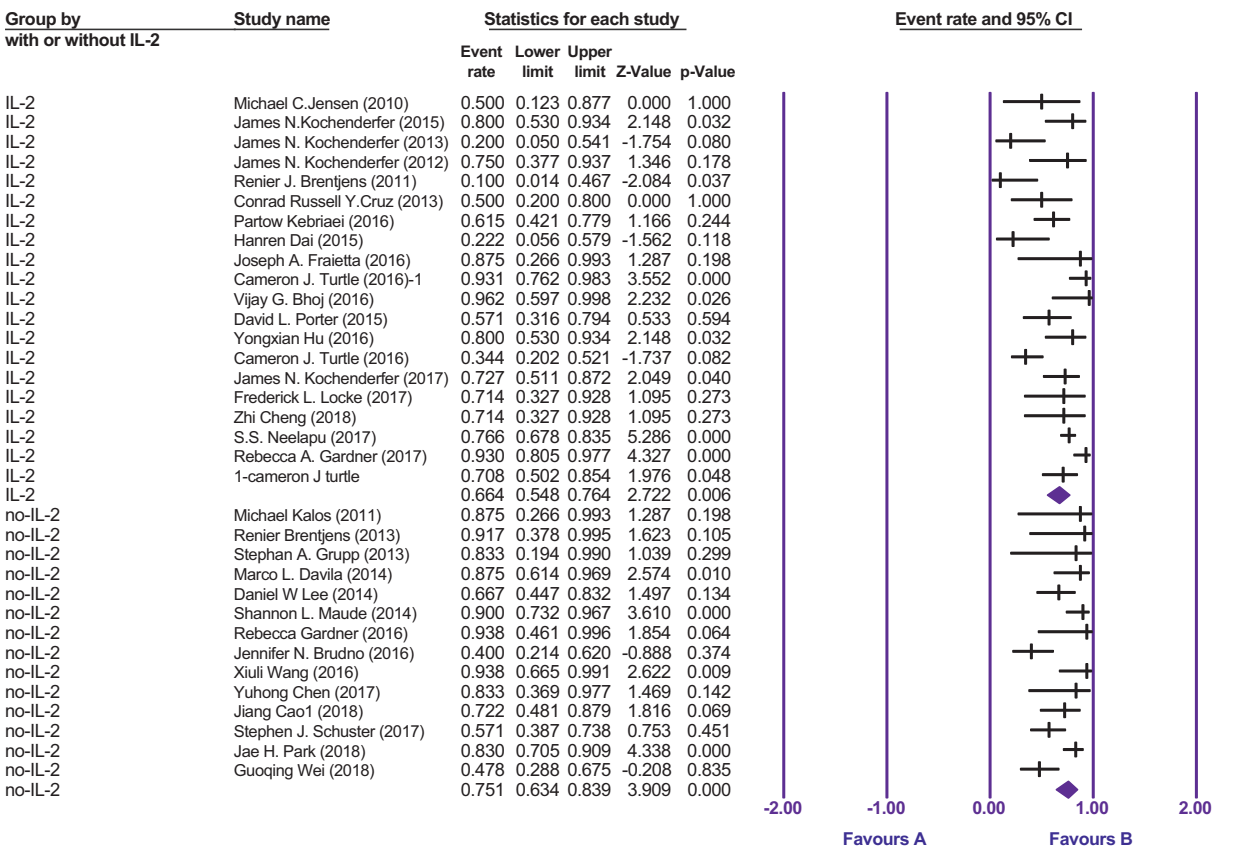


Figure 5. Forest plot showing RR in patients with or without IL-2 administration. A random effects meta-analysis model was used.

trials, differences in the type of chemotherapy used, dosage, and different inclusion and exclusion criteria across studies. These important variables must be considered when deriving inferences about efficacy and outcomes of individual trials. Our meta-analysis showed that CD19-CAR-T therapy is effective for the majority of aggressive hematological diseases such as ALL, CLL and lymphoma patients, but it also has certain contraindications.

We should point out that heterogeneity among the diseases could contribute to the inaccuracy of regression estimation in the whole population. To address the heterogeneity, we selected a random-effects model in each analysis (Figures 2–6). Furthermore, individual parameters such as patient factors (e.g., age, comorbidity), inclusion and exclusion criteria (e.g., CR and PR) and chemotherapy type could induce bias and influence association assessment and the quality of the meta-analysis.

In summary, clinical data presented by several preclinical research studies in the past several years herald a pioneering technical revolution, in both the management of B-cell malignancy and the development of CAR-T cell therapy as a new modality of cancer treatment. Our review includes 38 clinical trials and the largest number of patients (665) reported to date compared with the previous published systematic review. Our meta-analysis demonstrated a high clinical response rate of CD19-CAR-T cell–based immunotherapy in patients with refractory B-cell malignancies. This information will be helpful not only to further establish this approach in the treatment of hematological malignancies, but also to facilitate the application of this technology to solid tumor immunotherapy.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 31171427 and 30971651 to Zheng-Xu Wang); Beijing Municipal Science & Technology Project; Clinical characteristics and Application Research of Capital (No. Z121107001012136 to Zheng-Xu Wang); the National Natural Science Foundation of China (No. 30700974 to Jun-Xia Cao); the Postdoctoral

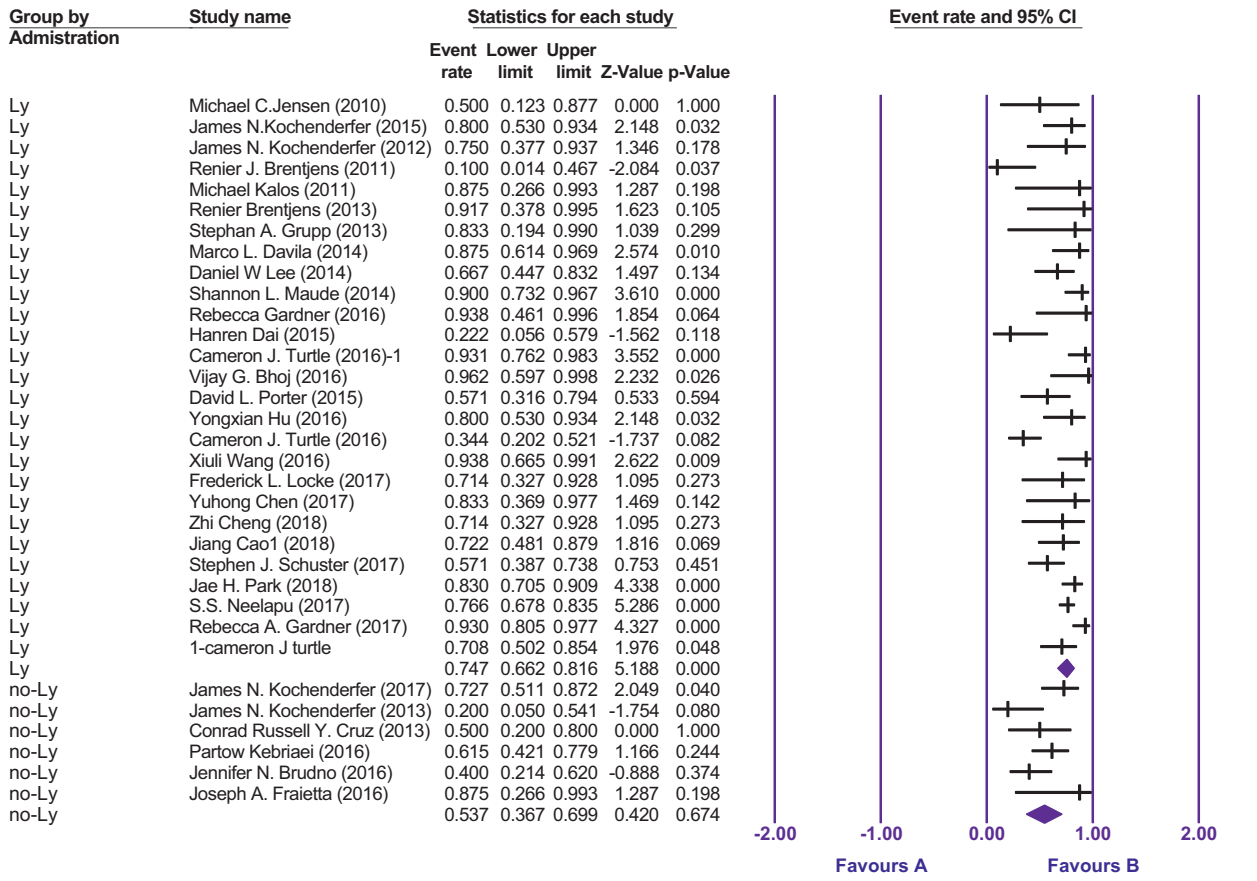


Figure 6. Forest plot for RR in patients with or without lymphodepletion before T-cell infusion. The random effects meta-analysis model was used. Ly, lymphodepletion; no-Ly, no lymphodepletion.

Foundation of China (No. 20060400775 to Jun-Xia Cao); The Seventh Medical Center of PLA General Hospital Innovation and Cultivation Fund (2016-PY-JC-004 to Jun-Xia Cao).

Disclosure of interest: The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

References

[1] McCreedy BJ, Senyukov VV, Nguyen KT. Off the shelf T cell therapies for hematologic malignancies. Best Pract Res Clin Haematol 2018;31(2):166–75. https://doi.org/10.1016/j.beha.2018.03.001. Epub 2018 Mar 28.

[2] Lichtman EI, Dotti G. Chimeric antigen receptor T-cells for B-cell malignancies. Transl Res 2017;187:59–82. https://doi.org/10.1016/j.trsl.2017.06.011. Epub 2017 Jun 29.

[3] Tasian SK, Gardner RA. CD19-redirected chimeric antigen receptor-modified T cells: a promising immunotherapy for children and adults with B-cell acute lymphoblastic leukemia (ALL). Ther Adv Hematol 2015;6(5):228–41. https://doi.org/10.1177/2040620715588916.

[4] Park JH, Geyer MB, Brentjens RJ. CD19-targeted CAR T-cell therapeutics for hematologic malignancies: interpreting clinical outcomes to date. Blood 2016;127(26):3312–20. https://doi.org/10.1182/blood-2016-02-629063. Epub 2016 May 20.

[5] Tran E, Longo DL, Urba WJ. A Milestone for CAR T Cells. N Engl J Med 2017;377(26):2593–6. https://doi.org/10.1056/NEJMe1714680. Epub 2017 Dec 10.

[6] Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018;378(5):439–48. https://doi.org/10.1056/NEJMoa1709866.

[7] Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017;377(26):2531–44. https://doi.org/10.1056/NEJMoa1707447. Epub 2017 Dec 10.

[8] Siddiqi T, Abramson JS, Palomba ML, Gordon LI, Lunning MA. Correlation of patient characteristics and biomarkers with clinical outcomes of JCAR017 in R/R aggressive B-NHL (TRANSCEND NHL 001 study). Journal of Clinical Oncology 2018;36(5_suppl). 122-122.

[9] Xu XJ, Zhao HZ, Tang YM. Efficacy and safety of adoptive immunotherapy using anti-CD19 chimeric antigen receptor transduced T-cells: a systematic review of phase I clinical

trials. Leuk Lymphoma 2013;54(2):255–60. https://doi.org/10.3109/10428194.2012.715350. Epub 2012 Sep 8.

[10] Zhu Y, Tan Y, Ou R, Zhong Q, Zheng L, Du Y, et al. Anti-CD19 chimeric antigen receptor-modified T cells for B-cell malignancies: a systematic review of efficacy and safety in clinical trials. Eur J Haematol 2016;96(4):389–96. https://doi.org/10.1111/ejh.12602. Epub 2015 Jul 3.

[11] Zhang T, Cao L, Xie J, Shi N, Zhang Z, Luo Z, et al. Efficiency of CD19 chimeric antigen receptor-modified T cells for treatment of B cell malignancies in phase I clinical trials: a meta-analysis. Oncotarget 2015;6(32):33961–71. https://doi.org/10.18632/oncotarget.5582.

[12] Riaz IB, Zahid U, Kamal MU, Husnain M, McBride A, Hua A, et al. Anti-CD 19 and anti-CD 20 CAR-modified T cells for B-cell malignancies: a systematic review and meta-analysis. Immunotherapy 2017;9(12):979–93. https://doi.org/10.2217/imt-2017-0062.

[13] Hao L, Li T, Chang LJ, Chen X. Adoptive immunotherapy for B-cell malignancies using CD19-targeted chimeric antigen receptor T-cells: A systematic review of efficacy and safety. Curr Med Chem 2017. https://doi.org/10.2174/0929867324666170801101842. [Epub ahead of print].

[14] Jin Z, Xiang R, Qing K, Li X, Zhang Y, Wang L, et al. The severe cytokine release syndrome in phase I trials of CD19-CAR-T cell therapy: a systematic review. Ann Hematol 2018. https://doi.org/10.1007/s00277-018-3368-8. [Epub ahead of print].

[15] Vormittag P, Gunn R, Ghorashian S, Veraitch FS. A guide to manufacturing CAR T cell therapies. Curr Opin Biotechnol 2018;53:164–81. https://doi.org/10.1016/j.copbio.2018.01.025. Epub 2018 Feb 18.

[16] Sharma P, King GT, Shinde SS, Purev E, Jimeno A. Axicabtagene ciloleucel for the treatment of relapsed/refractory B-cell non-Hodgkin's lymphomas. Drugs Today (Barc) 2018;54(3):187–98. https://doi.org/10.1358/dot.2018.54.3.2776625.

[17] Jensen MC, Popplewell L, Cooper LJ, DiGiusto D, Kalos M, Ostberg JR, Forman SJ. Antitransgene rejection responses contribute to attenuated persistence of adoptively transferred CD20/CD19-specific chimeric antigen receptor redirected T cells in humans. Biol Blood Marrow Transplant 2010;16(9):1245–56. https://doi.org/10.1016/j.bbmt.2010.03.014. Epub 2010 Mar 19.

[18] Kochenderfer JN, Dudley ME, Kassim SH, Somerville RP, Carpenter RO, Stetler-Stevenson M, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol 2015;33(6):540–9. https://doi.org/10.1200/JCO.2014.56.2025. Epub 2014 Aug 25.

[19] Kochenderfer JN, Wilson WH, Janik JE, Dudley ME, Stetler-Stevenson M, Feldman SA, et al. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. Blood 2010;116(20):4099–102. https://doi.org/10.1182/blood-2010-04-281931. Epub 2010 Jul 28.

[20] Kochenderfer JN, Dudley ME, Carpenter RO, Kassim SH, Rose JJ, Telford WG, et al. Donor-derived CD19-targeted T cells cause regression of malignancy persisting after allogeneic hematopoietic stem cell transplantation. Blood 2013;122(25):4129–39. https://doi.org/10.1182/blood-2013-08-519413. Epub 2013 Sep 20.

[21] Kochenderfer JN, Dudley ME, Feldman SA, Wilson WH, Spaner DE, Maric I, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. Blood 2012;119(12):2709–20. https://doi.org/10.1182/blood-2011-10-384388. Epub 2011 Dec 8.

[22] Brentjens RJ, Rivière I, Park JH, Davila ML, Wang X, Stefanski J, et al. Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. Blood 2011;118(18):4817–28. https://doi.org/10.1182/blood-2011-04-348540. Epub 2011 Aug 17.

[23] Kalos M, Levine BL, Porter DL, Katz S, Grupp SA, Bagg A, June CH. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. Sci Transl Med 2011;3(95):95ra73. https://doi.org/10.1126/scitranslmed.3002842.

[24] Savoldo B, Ramos CA, Liu E, Mims MP, Keating MJ, Carrum G, et al. CD28 costimulation improves expansion and persistence of chimeric antigen receptor-modified T cells in lymphoma patients. J Clin Invest 2011;121(5):1822–6. https://doi.org/10.1172/JCI46110. Epub 2011 Apr 11.

[25] Brentjens RJ, Davila ML, Riviere I, Park J, Wang X, Cowell LG, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Sci Transl Med 2013;5(177):177ra38. https://doi.org/10.1126/scitranslmed.3005930.

[26] Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, Teachey DT, Chew A, Hauck B, Wright JF, Milone MC, Levine BL, June CH. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med 2013;368(16):1509–18. https://doi.org/10.1056/NEJMoa1215134. Epub 2013 Mar 25.

[27] Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 2014;6(224):224ra25. https://doi.org/10.1126/scitranslmed.3008226.

[28] Lee DW, Kochenderfer JN, Stetler-Stevenson M, YK Cui 1, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385(9967):517–28. https://doi.org/10.1016/S0140-6736(14)61403-3. Epub 2014 Oct 13.

[29] Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014 Oct 16;371(16):1507–17. https://doi.org/10.1056/NEJMoa1407222.

[30] Cruz CR, Micklethwaite KP, Savoldo B, Ramos CA, Lam S, Ku S, et al. Infusion of donor-derived CD19-redirected virus-specific T cells for B-cell malignancies relapsed after allogeneic stem cell transplant: a phase 1 study. Blood 2013;122(17):2965–73. https://doi.org/10.1182/blood-2013-06-506741. Epub 2013 Sep 12.

[31] Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med 2011 Aug 25;365(8):725–33. https://doi.org/10.1056/NEJMoa1103849. Epub 2011 Aug 10.

[32] Gardner R, Wu D, Cherian S, Fang M, Hanafi LA, Finney O, et al. Acquisition of a CD19-negative myeloid phenotype allows immune escape of MLL-rearranged B-ALL from CD19 CAR-T-cell therapy. Blood 2016;127(20):2406–10. https://doi.org/10.1182/blood-2015-08-665547. Epub 2016 Feb 23.

[33] Kebriaei P, Singh H, Huls MH, Figliola MJ, Bassett R, Olivares S, et al. Phase I trials using Sleeping Beauty to generate CD19-specific CAR T cells. J Clin Invest 2016;126(9):3363–76. https://doi.org/10.1172/JCI86721. Epub 2016 Aug 2.

[34] Brudno JN, Somerville RP, Shi V, Rose JJ, Halverson DC, Fowler DH, et al. Allogeneic T Cells That Express an Anti-CD19 Chimeric Antigen Receptor Induce Remissions of B-Cell Malignancies That Progress After Allogeneic Hematopoietic Stem-Cell Transplantation Without Causing Graft-Versus-Host

Disease. J Clin Oncol 2016;34(10):1112–21. https://doi.org/10.1200/JCO.2015.64.5929. Epub 2016 Jan 25.

[35] Dai H, Zhang W, Li X, Han Q, Guo Y, Zhang Y, et al. Tolerance and efficacy of autologous or donor-derived T cells expressing CD19 chimeric antigen receptors in adult B-ALL with extramedullary leukemia. Oncoimmunology 2015;4(11):e1027469. eCollection 2015 Nov.

[36] Garfall AL, Maus MV, Hwang WT, Lacey SF, Mahnke YD, Melenhorst JJ, et al. Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma. N Engl J Med 2015;373(11):1040–7. https://doi.org/10.1056/NEJMoa1504542.

[37] Fraietta JA, Beckwith KA, Patel PR, Ruella M, Zheng Z, Barrett DM, et al. Ibrutinib enhances chimeric antigen receptor T-cell engraftment and efficacy in leukemia. Blood 2016;127(9):1117–27. https://doi.org/10.1182/blood-2015-11-679134. Epub 2016 Jan 26.

[38] Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest 2016;126(6):2123–38. https://doi.org/10.1172/JCI85309. Epub 2016 Apr 25.

[39] Bhoj VG, Arhontoulis D, Wertheim G, Capobianchi J, Callahan CA, Ellebrecht CT, et al. Persistence of long-lived plasma cells and humoral immunity in individuals responding to CD19-directed CAR T-cell therapy. Blood 2016;128(3):360–70. https://doi.org/10.1182/blood-2016-01-694356. Epub 2016 May 10.

[40] Porter DL, Hwang WT, Frey NV, Lacey SF, Shaw PA, Loren AW, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Sci Transl Med 2015;7(303):303ra139. https://doi.org/10.1126/scitranslmed.aac5415.

[41] Hu Y, Wu Z, Luo Y, Shi J, Yu J, Pu C, et al. Potent Anti-leukemia Activities of Chimeric Antigen Receptor-Modified T Cells against CD19 in Chinese Patients with Relapsed/Refractory Acute Lymphocytic Leukemia. Clin Cancer Res 2017;23(13):3297–306. https://doi.org/10.1158/1078-0432.CCR-16-1799. Epub 2016 Dec 30.

[42] Turtle CJ, Haafi LA, Berger C, Hudecek M, Pender B, Robinson E, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med 2016;8(355):355ra116. https://doi.org/10.1126/scitranslmed.aaf8621.

[43] Wang X, Popplewell LL, Wagner JR, Naranjo A, Blanchard MS, Mott MR, et al. Phase 1 studies of central memory-derived CD19 CAR T-cell therapy following autologous HSCT in patients with B-cell NHL. Blood 2016;127(24):2980–90. https://doi.org/10.1182/blood-2015-12-686725. Epub 2016 Apr 26.

[44] Kochenderfer JN, Somerville RPT, Lu T, Shi V, Bot A, Rossi J, et al. Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated With High Serum Interleukin-15 Levels. J Clin Oncol 2017;35(16):1803–13. https://doi.org/10.1200/JCO.2016.71.3024. Epub 2017 Mar 14.

[45] Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, et al. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Mol Ther 2017;25(1):285–95. https://doi.org/10.1016/j.ymthe.2016.10.020. Epub 2017 Jan 4.

[46] Chen Y, Cheng Y, Suo P, Yan C, Wang Y, Chen Y, et al. Donor-derived CD19-targeted T cell infusion induces minimal residual disease-negative remission in relapsed B-cell acute lymphoblastic leukaemia with no response to donor lymphocyte infusions after haploidentical haematopoietic stem cell transplantation. Br J Haematol 2017;179(4):598–605. https://doi.org/10.1111/bjh.14923. Epub 2017 Oct 26.

[47] Cheng Z, Wei R, Ma Q, Shi L, He F, Shi Z, et al. In Vivo Expansion and Antitumor Activity of Coinfused CD28- and 4-1BB-Engineered CAR-T Cells in Patients with B Cell Leukemia. Mol Ther 2018;26(4):976–85. https://doi.org/10.1016/j.ymthe.2018.01.022. Epub 2018 Feb 2.

[48] Cao J, Wang G, Cheng H, Wei C, Qi K, Sang W, et al. Potent anti-leukemia activities of humanized CD19-targeted Chimeric antigen receptor T (CAR-T) cells in patients with relapsed/refractory acute lymphoblastic leukemia. Am J Hematol 2018;93(7):851–8. https://doi.org/10.1002/ajh.25108. Epub 2018 Apr 28.

[49] Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak Ö, et al. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. N Engl J Med 2017;377(26):2545–54. https://doi.org/10.1056/NEJMoa1708566. Epub 2017 Dec 10.

[50] Park JH, Rivière I, Gonen M, Wang X, Sénéchal B, Curran KJ, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. N Engl J Med 2018;378(5):449–59. https://doi.org/10.1056/NEJMoa1709919.

[51] Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017;377(26):2531–44. https://doi.org/10.1056/NEJMoa1707447. Epub 2017 Dec 10.

[52] Wei G, Hu Y, Pu C, Yu J, Luo Y, Shi J, et al. CD19 targeted CAR-T therapy versus chemotherapy in re-induction treatment of refractory/relapsed acute lymphoblastic leukemia: results of a case-controlled study. Ann Hematol 2018;97(5):781–9. https://doi.org/10.1007/s00277-018-3246-4. Epub 2018 Feb 7.

[53] Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood 2017;129(25):3322–31. https://doi.org/10.1182/blood-2017-02-769208. Epub 2017 Apr 13.

[54] Turtle CJ, Hay KA, Hanafi LA, Li D, Cherian S, Chen X, Wood B, Lozanski A, Byrd JC, Heimfeld S, Riddell SR, Maloney DG. Durable Molecular Remissions in Chronic Lymphocytic Leukemia Treated With CD19-Specific Chimeric Antigen Receptor-Modified T Cells After Failure of Ibrutinib. J Clin Oncol 2017;35(26):3010–20. https://doi.org/10.1200/JCO.2017.72.8519. Epub 2017 Jul 17.

[55] Zhou H, Luo Y, Zhu S, Wang X, Zhao Y, Ou X, et al. The efficacy and safety of anti-CD19/CD20 chimeric antigen receptor- T cells immunotherapy in relapsed or refractory B-cell malignancies:a meta-analysis. BMC Cancer 2018;18(1):929. https://doi.org/10.1186/s12885-018-4817-4.

[56] Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science 2015;348(6230):62–8. https://doi.org/10.1126/science.aaa4967.

[57] Brudno JN, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. Nat Rev Clin Oncol 2018;15(1):31–46. https://doi.org/10.1038/nrclinonc.2017.128. Epub 2017 Aug 31.

[58] Anwer F, Shaukat AA, Zahid U, Husnain M, McBride A, Persky D, et al. Donor origin CAR T cells: graft versus malignancy effect without GVHD, a systematic review. Immunotherapy 2017;9(2):123–30. https://doi.org/10.2217/imt-2016-0127.