REVIEW ARTICLE

Strategies to optimize chimeric antigen receptor T-cell therapy in hematologic malignancies: Chinese experience

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy has emerged as a promising form of adoptive T-cell immunotherapy for selected hematologic malignancies including leukemia, lymphoma and multiple myeloma. China has become the country with the largest number of registered CAR T-cell trials. Despite the remarkable clinical outcomes achieved with CAR T-cell therapy, challenges such as disease relapse, the process of manufacturing the CAR T cells and safety have limited the therapeutic efficacy of CAR T cells in hematologic malignancies. In this period of innovation, several clinical trials have reported the design of CAR directed at new targets in hematologic malignancies. In this review, we comprehensively summarize the contemporary landscape and clinical development of CAR T-cell therapy in China. In addition, we present strategies for further improving the clinical utility of CAR T-cell therapy, such as increasing the efficacy and response duration, in hematologic malignancies.

Introduction

Over the past few decades, treatment strategies for hematologic malignancies have made tremendous headway. However, the morbidity and mortality rates attributed to these malignancies remain substantial.[1] Advances in molecular genetics have paved the way for further in-depth understanding of the interaction between the immune system and cancer cells and revealed the great potential of T cells for use in immunotherapy of hematologic malignancies.[1] At this breakthrough juncture, multiple iterations of adoptive cell therapies have been designed to overcome immune evasion mechanisms in cancer by directly targeting cancer cells and activating specific immune responses to tumors.[2] One such adoptive T-cell-centered immunotherapy, which has been successfully translated from bench to bedside, is genetically engineered chimeric antigen receptors (CAR) that can recognize cancer-associated antigens, leading to T-cell activation, proliferation and memory.[2] CAR T-cell therapies engineered against different tumor antigens have shown astonishing efficacy and durable clinical responses in many types of malignancies, especially hematopoietic ones such as acute lymphoblastic leukemia (ALL), large B-cell lymphoma (LBCL) and multiple myeloma (MM), and have revolutionized the therapeutic landscape of cancer immunotherapy. Moreover, given their great potential for continuous optimization, CAR T-cell therapies are attractive replacements of conventional therapies (chemotherapy, radiation therapy, stem cell transplantation) as new targets continue to emerge. Approval of two CAR T-cell products, tisagenlecleucel (Kymriah) for the treatment of B-cell ALL (B-ALL) in pediatric and young adult patients (aged ≤25 years)[3] and axicabtagene ciloleucel (Yescarta) for the treatment of LBCL[4] in adult patients by the USA Food and Drug Administration (FDA) in 2017 was a milestone in the history of cancer research. In 2022, ciltacabtagene autoleucel (Carvykti) was approved by the FDA for the treatment of patients with MM, becoming the sixth approved CAR T-cell therapy.

Due to the remarkable success of CAR T-cell therapy, the number of clinical trials on this treatment has increased rapidly across the globe, with USA and China being the major forces contributing to about 33% of all such trials. In China, T-cell immunotherapy has been widely used for treating cancer, and several studies have revealed the remarkable antitumor effects of CAR T cells. These findings inspired researchers from China to implement further domestic CAR T-cell trials and clinical trials on precision im-

munotherapy (CAR T-cell therapy) have expanded rapidly in the country, which has taken the place of the USA as the nation with the most CAR T-cell studies (~444 as of 2021) and nowadays plays a paramount role in developing innovative strategies for CAR T-cell therapy. In this review, we comprehensively describe the current status of CAR T-cell trials in China. In addition, we present an updated overview of CAR T-cell therapeutic options in hematologic malignancies, as well as strategies to improve the efficacy and safety of CAR T-cell therapy, which will have a tremendous impact on the field of T-cell immunotherapy.

Approval of chimeric antigen receptor T-cell therapies in China

Axicabtagene ciloleucel was the first commercially available autologous CD19-directed CAR T-cell therapy approved in China for the treatment of adult patients with relapsed or refractory (r/r) LBCL, including diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy. The approval was based on the results of a single-arm, open-label, multicenter bridging trial (FKC876-2018-001) ChiCTR1800019661, in which 79.2% of patients achieved a response after a single infusion of axicabtagene ciloleucel.[5] Relmacabtagene autoleucel (Carteyva) was the second approved CD19-targeting CAR construct for the treatment of LBCL after at least two prior lines of systemic therapy.[6] The approval was based on the findings of the RELIANCE study, in which patients with r/r LBCL who failed at least two lines of therapy were treated with relmacabtagene autoleucel. The overall response rate (ORR) was 75.9%, with a complete response (CR) rate of 51.7% and a 12-month overall survival rate of 76.8% (as of June 17, 2020, the data cutoff).[7] Table 1 summarizes the CAR T-cell therapies approved by the Chinese National Medical Products Administration (NMPA) or FDA, with data updated to March 2022.

Overview and characteristics of the clinical development of chimeric antigen receptor T-cell therapy in China

We retrieved clinical trials on CAR T-cell therapy from the ClinicalTrials.gov website using the keywords “CAR T” or “CAR-T” or “chimeric antigen receptor T cell” or “chimeric

Table 1. Chimeric antigen receptor T-cell products approved by the American Food and Drug Administration or the Chinese National Medical Products Administration.

Product name	Manufacturer	Approval agency/year	Indication	Trial name/ID
Tisagenlecleucel (Kymriah®)	Novartis	FDA/2017	Children and young adults (aged ≤25 years) with r/r ALL	ELIANA/ NCT02435849
Tisagenlecleucel (Kymriah®)	Novartis	FDA/2018	r/r DLBCL	JULIET/ NCT02445248
Axicabtagene ciloleucel (Yescarta®)	Kite	FDA/2017	r/r DLBCL	ZUMA-1/ NCT02348216
Axicabtagene ciloleucel (Yescarta®)	Kite	FDA/2021	r/r FL	ZUMA-5/ NCT03105336
Brexucabtagene autoleucel (Tecartus®)	Kite	FDA/2020	r/r MCL	ZUMA-2/ NCT02601313
Brexucabtagene autoleucel (Tecartus®)	Kite	FDA/2021	r/r B-ALL	ZUMA-3/ NCT02614066
Lisocabtagene marleucel (Breyanzi®)	Juno Therapeutics	FDA/2021	r/r LBCL	TRANSCEND NHL001/ NCT02631044
Idecabtagene vicleucel (Abecma®)	Bristol Myers Squibb	FDA/2021	r/r MM	KarMMA study/ NCT03361748
Ciltacabtagene autoleucel (Carvykti®)	Nanjing Legend Bio and Janssen	FDA/2022	r/r MM	CARTITUDE-1/ NCT03548207
Axicabtagene ciloleucel (Yescarta®)	Fosun Kite Biotechnology	NMPA/2021	r/r DLBCL	ChiCTR1800019661
Relmacabtagene autoleucel (Carteyva®)	JW Therapeutics	NMPA/2021	r/r LBCL	NCT04089215

ID: identity; FDA: Food and Drug Administration; NMPA: National Medical Products Administration; r/r: relapsed/refractory; ALL: acute lymphoblastic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; MCL: mantle cell lymphoma; B-ALL: B-cell acute lymphoblastic leukemia; LBCL: large B-cell lymphoma; MM: multiple myeloma.

antigen receptor", followed by manual verification to exclude the non-CAR T-cell therapy trials. As of December 2022, there were 458 trials from China reported and/or registered at ClinicalTrials.gov. The majority involved investigations on hematologic malignancies (73%, n=337) followed by solid tumors (24%, n=111) (Figure 1A). Since research on CAR T-cell therapy is mainly distributed in China and the USA, we also compared the clinical trials in the two countries. While the percentages of trials were comparable between China and the USA, China has a greater number of trials registered than the USA across all tumor types (Figure 1A). In comparison to Chinese CAR T-cell therapy clinical trials in hematologic malignancies, which started in 2012, such trials started in 2009 in the USA. The number of trials in hematologic malignancies was comparable in the two countries between 2012 and 2015, and then in 2016 China surpassed the USA in number of CAR T-cell clinical studies in hematologic malignancies and is still leading (Figure 1B). In terms of the distribution of the phase of the trials, the same trend was seen in China and the USA with the highest percentage of trials being phase I trials and the lowest percentage being phase III trials. As regard to the sample size of the clinical studies on CAR T-cell therapy in hematologic malignancies, this varied between 10-30 patients in China with only a few studies recruiting approximately 100 patients. In contrast, a higher proportion of trials in the USA had a sample size of >30 patients (Figure 1C, D).

CD19 and B-cell maturation antigen (BCMA) are the most common antigens being targeted in China, with a total of 127 and 36 trials, respectively, in hematologic malignancies. A similar trend was observed in trials in hematologic malignancies in the USA (Figure 2A, B). While CD7 (17 trials) has been more investigated in Chinese CAR T-cell trials in hematologic malignancies, CD4 (2 trials) and CD33 (3 trials) have been studied more frequently in trials in the USA (Figure 2A, B). Compared with the USA, China has a higher proportion of trials involving the use of multi-target (≥2) CAR T cells. Most of the multi-target CAR T-cell clinical trials in hematologic malignancies in China have involved the combination of CD19 and CD22 (25 trials) followed by CD19 combined with CD20 (17 trials). The multi-agent trials in the USA have also most commonly involved the same targets (Figure 2C, D). Meanwhile, Chi-

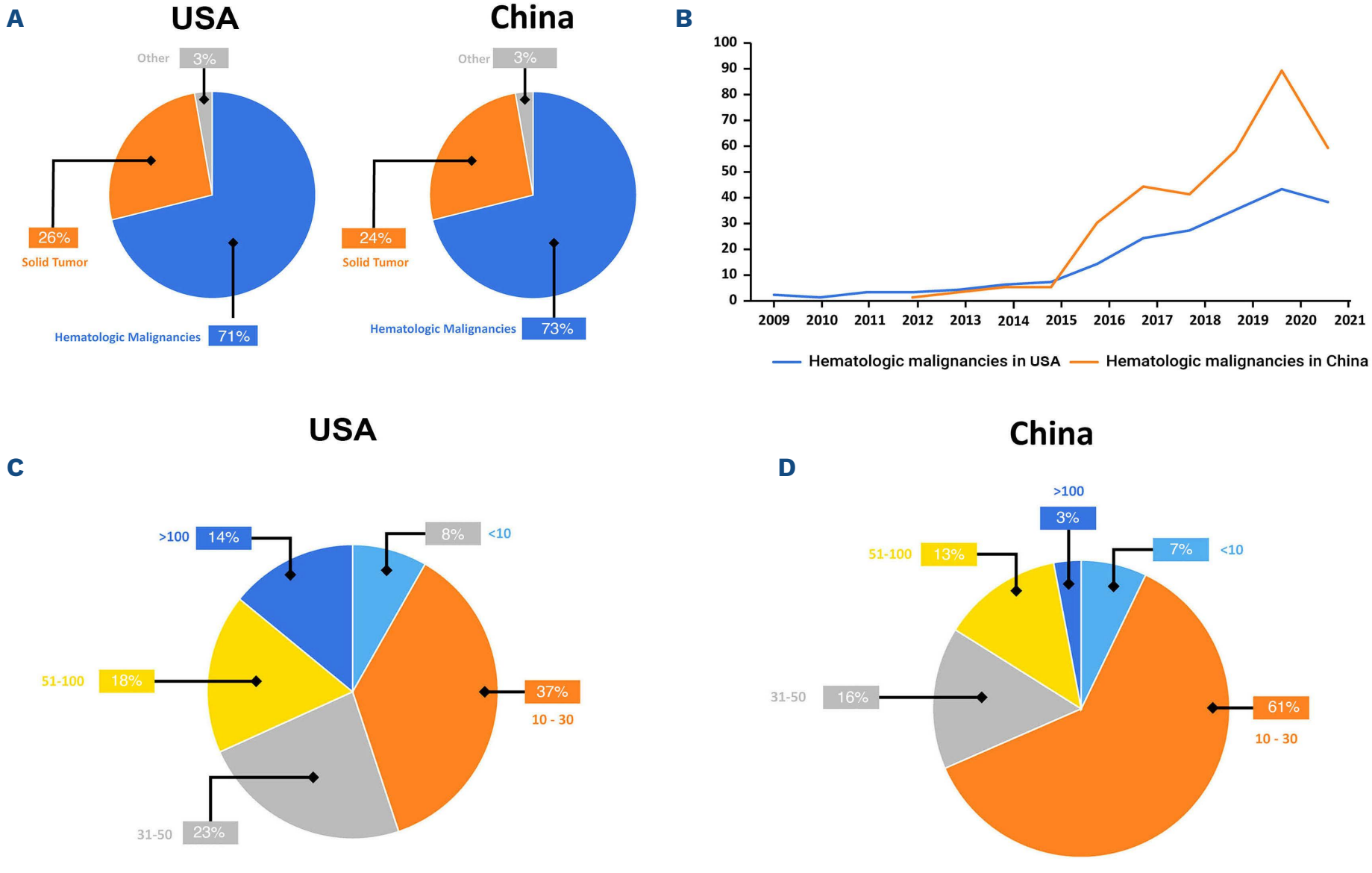


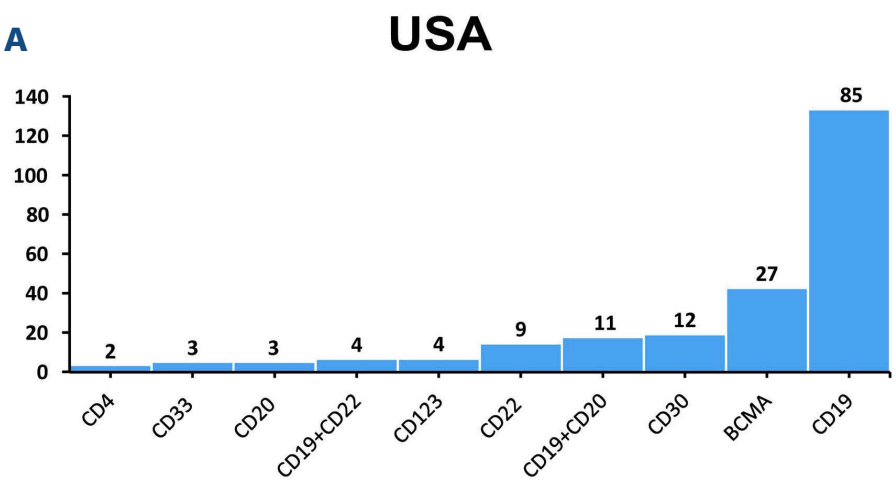
Figure 1. Overview of the clinical development of chimeric antigen receptor T-cell therapy and trials in hematologic malignancies. (A) Proportions of chimeric antigen receptor (CAR) T-cell clinical trials in hematologic and solid tumors in China and the USA. (B) Number of CAR T-cell clinical trials in hematologic malignancies in China and the USA from 2009-2021. (C, D) The percentages of CAR T-cell trials in hematologic malignancies by number of patients enrolled in the USA (C) and in China (D).

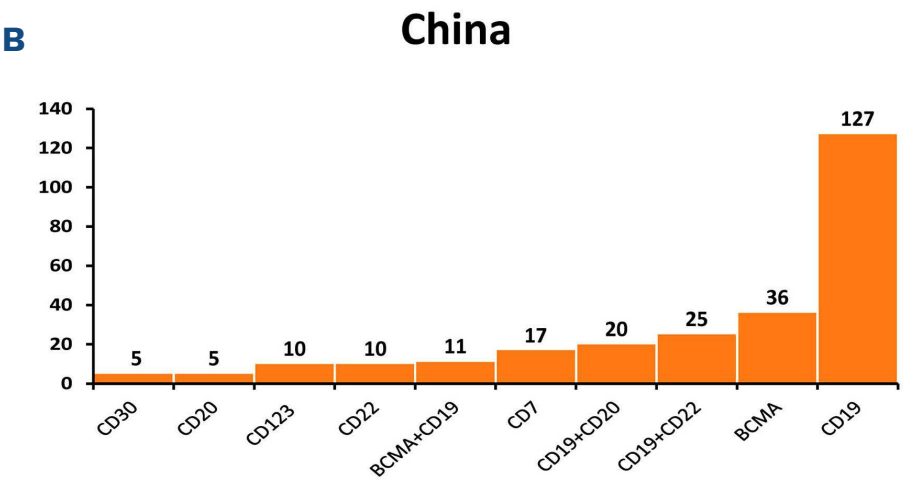
nese researchers have more frequently explored CAR T-cell therapy with BCMA combined with another target.

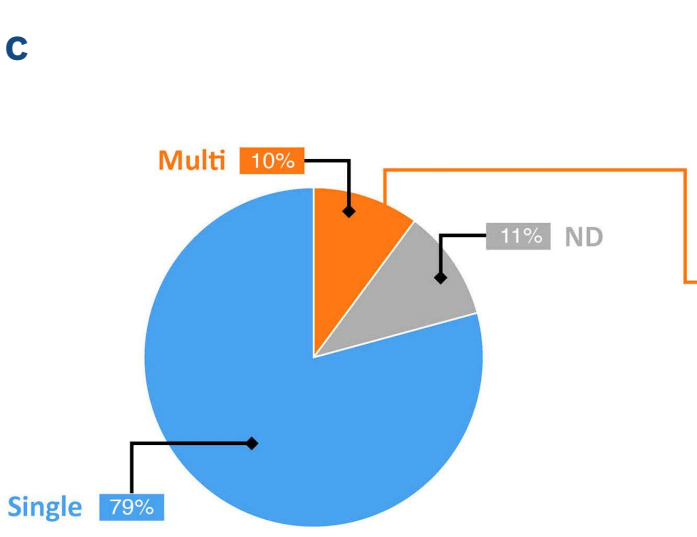
Concomitant treatments used along with CAR T-cell therapy were somewhat similar between the USA and China with the major differences being the use of chidamide/decitabine (2 trials) and dasatinib (1 trial) in leukemia/lymphoma and MM trials in China *versus* PI3Kδ/γ inhibitors (1 trial) and bi-specific antibodies (1 trial) used in leukemia/lymphoma trials and immunomodulatory imide drugs, γ-secretase inhibitors and antibody-drug conjugates used in MM in trials in the USA (Figure 3A-D).

Strategies to improve the efficacy of chimeric antigen receptor T-cell therapy: Chinese experience

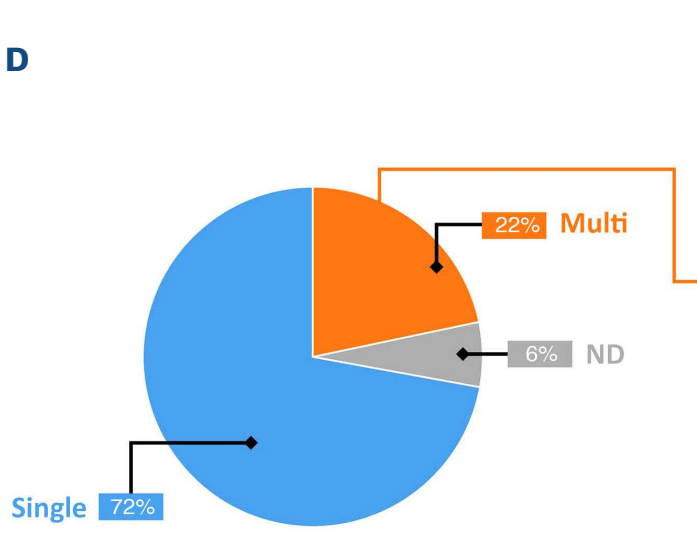
In China, although CAR T-cell therapy has entered the therapeutic arsenal for hematologic malignancies and it has demonstrated efficacy in leukemia, lymphoma and MM, approximately 30-60% of cases relapse after this therapy.[8] In addition, CAR T-cell therapy has several shortcomings such as difficulties in identifying ideal target tumor antigens, inhibition and resistance, antigen escape, decreased persistence and expansion of CAR T cells, sus-







Multi-targets used in CAR T	Number of trials
CD19+CD20	9
CD19+CD22	7
CD1+/CD20+CD22	2
CD19+CD28	1
CD30+CCR4	1
CD79a+CD20	1



Multi-targets used in CAR T	Number of trials
CD19+CD22	25
CD19+CD20	17
CD19+BCMA	11
CD19+other target	9
BCMA+other target	5
Other	7

Figure 2. Antigen targets of chimeric antigen receptor T-cell therapy in hematologic malignancies. (A, B) Top ten targets of chimeric antigen receptor (CAR) T-cell therapy in hematologic malignancies in the USA (A) and in China (B). (C, D) Multi-targets used in CAR T cells in hematologic malignancies in the USA (C) and in China (D). BCMA: B-cell maturation antigen; ND: no data.

ceptibility of CAR T cells to an immunosuppressive microenvironment, limited efficacy during rescue therapy, and life-threatening toxicities. These problems associated with CAR T cells still exist and pose enormous challenges, because they undermine the prospective efficacy and durability of CAR T cells.[9] Several strategies are currently under investigation to address these problems. In this section, we summarize the current status of clinical development of CAR T-cell therapy in leukemia, lymphoma and MM in China (Tables 2-7).[10-58] Furthermore, we detail a series of promising strategies to optimize the curative effect of CAR T-cell therapy (Figure 4).

Acute lymphoblastic leukemia

ALL is a hematologic malignancy that originates from malignant precursor B or T lymphocytes with a morbidity rate of 0.69 per 100,000 persons in China.[9] With conventional chemotherapy and standardized intensive therapies, many patients still suffer from r/r disease, with a relapse rate of 15-20% in pediatric B-ALL and 50% in adult B-ALL. Indeed, r/r disease still remains a major obstacle in the therapy of ALL.

In China, the first CAR T-cell therapy for B-ALL targeting CD19 was reported in 2013, further studies have developed rapidly with the greatest efficacy of CD19-targeted CAR T-cell therapy demonstrated in r/r B-ALL. Although it is hoped that CAR T cells targeting CD19 will provide an additional CR for most r/r patients, durable remissions are difficult to achieve due to subsequent relapses.[59] Because resistance and relapse are intractable issues that preclude further development of CAR T-cell therapy in ALL, strategies to improve the efficacy of CAR T cells and repeated treatment after recurrence need to be considered. Toxicities and safety events may also prevent patients from benefiting from CAR T-cell therapy.

Autologous CAR T-cell therapy has been susceptible to failure as a consequence of limited quantity (in patients receiving lymphodepletion and/or chemotherapy) and poor

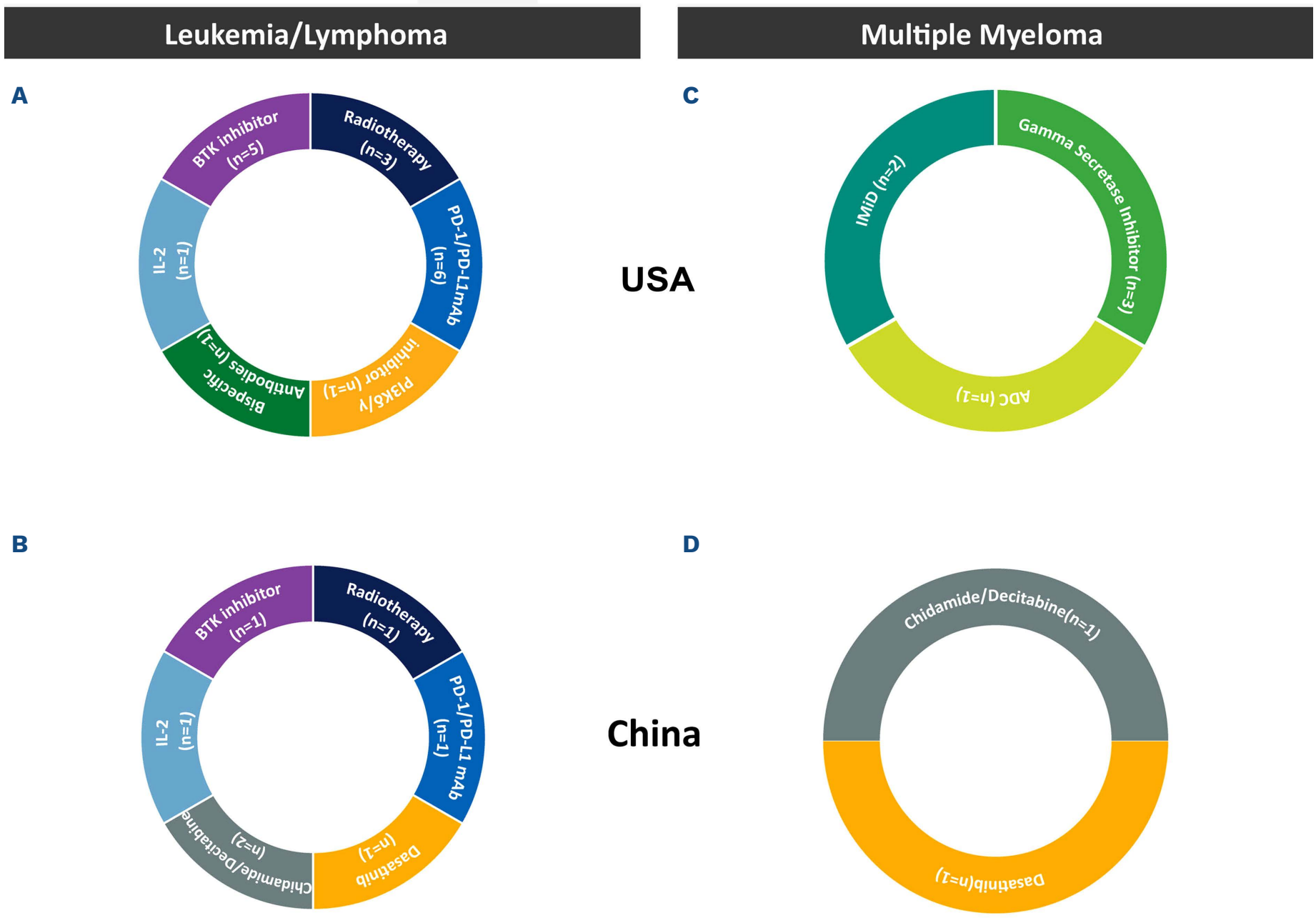


Figure 3. Different combination treatments used together with chimeric antigen receptor T cells. (A, B) Different combination treatments used together with chimeric antigen receptor (CAR) T cells in leukemia trials in the USA (A) and in China (B). (C, D) Different combination treatments used together with chimeric CAR T cells in multiple myeloma trials in the USA (C) and in China (D). PD-1: programmed cell death protein 1; PD-L1: programmed death ligand 1; mAb: monoclonal antibody; PI3K: phosophoinositide 3-kinase; IL-2: interleukin-2; BTK: Bruton tyrosine kinase; ADC: antibody-drug conjugate; IMiD: immunomodulatory drug.

Table 2. Chimeric antigen receptor T-cell therapy in leukemia: overview of current strategies to enhance efficacy.

Strategy	CAR T-cell/object	Trial ID	Phase	Key findings	Ref.
Alternative targets	CD22 CAR T-cell	ChiCTR-OIC-17013523	-	CR or CRi was achieved in 24 of 30 evaluable r/r B-ALL patients in whom previous CD19 CAR T-cell therapy had failed.	10
Multiple targets	Bi-specific CAR T cells targeting CD19 and CD22	NCT03185494	I	Following bi-specific CD19/CD22 CAR T-cell therapy, all 6 r/r B-ALL patients experienced MRD-negative CR.	11
	Sequential CD19/CD22 CAR T cells	ChiCTR-OIB-17013670	I	Seventeen of 20 pediatric patients with r/r B-ALL remained in remission at the cutoff date, resulting in a leukemia-free survival rate of 79.5% at 12 months.	12
	Combination of CD19 and CD22 CAR T cells	ChiCTRONC-17013648	I	Combination strategy of sequential CD19 and CD22 CAR T-cell therapy significantly improved the long-term survival (OS and EFS rates were 88.5% and 67.5%, respectively) in B-ALL patients who relapsed after transplantation.	13
CAR structure	CD19 CAR T cells containing CD28 or 4-1BB	NCT02349698	I/II	Both CD28 and 4-1BB CAR T cells produced responses, although they differed for response pattern (peak reaction time, reaction lasting time and reaction degree), adverse events, cytokine secretion and level of immune-suppressive factors.	14
	4-1BB- or CD28-based CD19 CAR T cells	NCT03173417	-	The performance of 4-1BB CAR T cells was superior to that of CD28 CAR T cells in suppressing $CD19^+$ B-ALL.	15
	Humanized CD19-targeted CAR T cells	NCT02782351	I	Among the 14 r/r ALL patients naïve to previous CAR T-cell therapy, 13 achieved CR or CRi on day 30, whereas 1 of the 3 patients who failed a second murine CAR T-cell infusion achieved CR after hCART19s infusion.	16
	Humanized selective CD19 CAR T cells	ChiCTR1800014761	I	Humanized selective CAR T cells were infused into 5 patients who had relapsed after receiving murine CAR T-cell treatments and 4 patients achieved molecular CR.	17
	CD19 CAR T cells binding to different CD19 epitopes	NCT02975687	Pilot study	90% of the 20 r/r B-ALL patients treated with infusions of CNCT19 cells reached CR or CRi within 28 days.	18
Combination therapy	Combination of decitabine and CAR T cells in r/r acute leukemia with *TP53* alterations	NCT03919240 NCT03614858 NCT03896854	II	Within 1 month after CAR T-cell infusions, 10 patients achieved CR and 9 achieved molecular CR.	19
Universal CAR T cells	CRISPR-edited universal off-the-shelf CD19/CD22 dual-targeted CAR T cells (CTA101)	NCT04227015	I	Six r/r ALL patients received CTA101 infusions. No dose-limiting toxicity, GvHD, neurotoxicity, or genome editing–associated adverse events have occurred to date. The CR rate was 83.3% on day 28 after CTA101 infusion.	20

CAR: chimeric antigen receptor; ID: identity; Ref: reference; CR: complete remission; CRi: complete remission with incomplete blood count recovery; r/r: relapsed/refractory; B-ALL: B-cell acute lymphoblastic leukemia; MRD: minimal residual disease; OS: overall survival; EFS: event-free survival; hCART19s: humanized CD19-specific CAR T cells; GvHD: graft-*versus*-host disease.

Table 3. Chimeric antigen receptor T-cell therapy in leukemia: overview of current strategies to enhance safety.

Strategy	CAR T cells/object	Trial ID	Phase	Key findings	Ref.
Monitor/ biomarker	Real-time monitoring of Th1/Th2 cytokine pattern using cytometric bead array technology	-	-	CD19 CAR T-cell therapy can be safely administered to patients with relapsed and refractory leukemia under "real-time" monitoring of a simple 6- Th1/Th2 cytokine pattern.	21
Virus reactivation	Efficacy and safety of CAR T-cell therapy in patients with concomitant HBV infection	NCT02822326	-	CAR T cells from HBV-positive patients exerted potent antileukemia effects without inducing HBV reactivation under close monitoring of HBV DNA and liver function.	22
CRS management	Using corticosteroids instead of tocilizumab as the first-line agent to manage CRS	ChiCTR-OIC-17013623, ChiCTR-ONC-17013648, ChiCTR-OIC-17013523	-	Corticosteroids did not influence the efficacy and kinetics of CAR T cells for B-ALL.	23

CAR: chimeric antigen receptor; ID: identity; Ref: reference; Th: T helper cell; HBV: hepatitis B virus; CRS: cytokine release syndrome; B-ALL: B-cell acute lymphoblastic leukemia.

quality (due to apheresis); therefore, allogeneic CAR T-cell therapy has become an attractive replacement. Nevertheless, allogeneic CAR T-cell therapy has its own challenges, such as graft-*versus*-host disease (GvHD) and graft rejection. Multiple studies have indicated that the failure of allogeneic CAR T-cell expansion related to GvHD and graft rejection in r/r ALL patients receiving allogeneic CD19-directed CAR T-cell therapy before or after allogeneic hematopoietic stem cell transplantation (HSCT) can be avoided or minimized. Zhang *et al.* presented the safety and efficacy of donor-derived anti-CD19 CAR T cells in 43 subjects with B-ALL relapsing after allotransplants: approximately 79% (n=34) patients achieved a CR. Two subjects had grade ≤2 acute GvHD.[60] On the other hand, Jin *et al.* described the first-in-human use of HLA-matched allogeneic CAR T cells (CD19-directed) before allogeneic HSCT: 75% (3/4) patients achieved a CR and no GvHD was observed.[61] Recent advances in allogeneic CAR T cells have focused on off-the-shelf products called universal CAR T cells. Huang *et al.* developed a CRISPR-edited universal off-the-shelf CD19/CD22 dual-targeted CAR T-cell product for the therapy of r/r ALL patients and documented that 83.3% (5/6) patients achieved minimal residual disease-negative CR with manageable adverse events.[20]

So far, the research on CAR T-cell therapy has been mainly focused on B-ALL, and there are relatively few studies on T-ALL. CD7 is highly expressed on the surface of T-ALL/T-cell lymphoblastic lymphoma T cells and is considered a viable CAR T-cell therapeutic target. In a single-center, phase I trial, Pan *et al.* administered anti-CD7 CAR T cells, manufactured from either previous stem-cell transplantation donors or new donors, to patients with r/r T-ALL, in whom the CR rate was 90% and adverse events were reversible.[62] Lu *et al.* described a novel approach using patient- or donor-derived “naturally selected” CD7-targeted CAR T cells (NS7CAR) without additional CD7 gene ablation or protein expression blockade. In their first-in-human, phase I trial (*clinicaltrials gov. Identifier: NCT04572308*), 20 patients with r/r T-ALL and T-cell lymphoblastic lymphoma were treated with NS7CAR. Nineteen patients achieved minimal residual disease-negative CR in the bone marrow by day 28, and five of nine patients achieved extramedullary CR.[63] These results indicate that CD7 CAR T-cell therapy is a safe and highly effective treatment for T-ALL. More patients and longer follow-up are needed for validation.

It should be noted that 10-30% of B-ALL patients relapse because of antigen escape (antigen-negative relapse). However, another common cause is the loss of CAR T cells, leading to antigen-positive relapse. In antigen-positive relapse, the components of CAR constructs (co-stimulatory domains and scFv) can influence the potency and persistence of CAR T cells. Several studies identified the therapeutic potential of anti-CD19 CAR containing either CD28 or 4-1BB co-stimulatory signaling in ALL, and the results hinted that 4-1BB-based CAR T cells have greater efficacy (as a result of stronger persistence) than CD28-based CAR T cells. Chen *et al.* recently initiated a trial with third-generation CD19 CAR T cells, combining 4-1BB and CD28 signaling domains, in the treatment of adults with r/r B-ALL: the results are awaited.[64] In addition, numerous studies have shown the therapeutic potential of humanized scFv CD19-targeted CAR T-cell therapy in B-ALL patients with no response or who relapsed after prior murine CD19 CAR T-cell therapy. Furthermore, CD19 CAR T cells with scFv capable of binding to different CD19 epitopes may provide an alternative for patients who undergo CD19-positive relapse. Wang *et al.* described a new CD19 CAR T-cell with a scFv that interacts with an epitope of the human CD19 antigen that is distinct from that recognized by the current FMC63 clone. This approach may be an alternative choice for some patients,

Table 4. Chimeric antigen receptor T-cell therapy in lymphoma: overview of current strategies to enhance efficacy.

Strategy	CAR T cells/object	Trial ID	Phase	Key findings	Ref.
Alternative targets	CD30 CAR T cells	ChiCTR-OPN-16009069	-	The median PFS was 13 months, with 3 long-term CR over 2 years.	24
	CD22 CAR T cells	ChiCTR-ONN-16009862	-	Four r/r DLBCL patients obtained CR, 2 r/r DLBCL patients achieved PR and 1 patient achieved SD. Only 2 r/r B-ALL patients obtained CRi.	25
Multiple targets	Co-administration of CD19 and CD20 CAR T cells	NCT03207178	II	Among 21 included patients, the ORR was 81.0% with 4 cases of bulk (4/5) and 1 case of testis involvement; 52.4% had a CR.	26
	CD19/22 CAR T-cell cocktail	ChiCTR-OPN-16008526	-	The ORR at 3 months after CAR T cells was 83.3% (10/12), including 3 CR (25%) and 7 PR (58.3%).	27
	Tandem CD19/CD20 CAR T cells	NCT03097770	I/IIa	Twenty-eight patients received of CAR T-cell infusion. The ORR was 79%, and the CR rate was 71%. PFS rate at 12 months was 64%.	28
	CD19/22 CAR T-cell cocktail	ChiCTR-OPN-16008526	-	Three patients achieved an objective response (3/6, 50%), including 2 PR and 1 CR.	29
	Sequential different B-cell antigen-targeted CAR T cells	ChiCTR18000144 57	I	The estimated 18-month CR rate was 78%. The estimated 18-month PFS rate was 78%.	30
	CD19/CD22 dual-targeted CAR T cells	ChiCTR1800015575	-	Fourteen patients (87.5%) achieved an objective response and 10 (62.5%) achieved CR. The 2-year OS and PFS rates were 77.3% and 40.2%, respectively.	31
	CD19/22 bi-specific CAR T cells	NCT03196830	-	The ORR was 79.3%, and the CR rate was 34.5%. The PFS and OS rates at 12 months were 40.0% and 63.3%, respectively.	32
CAR structure	Dominant-negative PD-1 armored CD19 CAR T cells	ChiCTR1900021295	I	The ORR was 77.8% (N=7/9) and the CR rate was 55.6% (N=5/9).	33
	CD19 CAR T expressing PD-1/CD28	-	-	Three of 6 patients achieved a CR. The duration of the response among responsive patients ranged from 8 to 25 months.	34
	CD19 CAR T cells expressing PD-1/CD28	-	Ib	Ten patients had an objective response (58.8%), including 7 CR (41.2%). No severe neurological toxicity or cytokine release syndrome was observed.	35
	4-1BB or CD28 co-stimulated CAR T-cell	NCT03528421	I/IIa	CD19-targeted CAR T cells with CD28 or 4-1BB showed similar antitumor efficacy.	36
	Fourth generation CAR	ChiCTR-OOC- 16007779	I	In 21 patients who received 4SCAR19 T-cell infusions, the ORR was 67%; 43% and 24% of patients achieved a CR and PR, respectively.	37
Combination therapy	CD19 CAR T cells with decitabine	-	-	Two patients with r/r B-cell lymphoma were pretreated with decitabine then treated with CD19 CAR T cells, and both achieved CR.	38
	CD19 CAR T cells with nivolumab	ChiCTR-ONN-16009862	-	ORR and CR rates were 81.81% and 45.45%, respectively. The median PFS was 6 months.	39
	CD19 CAR T cells with ibrutinib	ChiCTR-ONN-16009862	-	Three MCL patients and 3 FL patients reached CR and 1 FL patient reached PR.	40
	CD19/CD22 CAR T-cell cocktail following ASCT	ChiCTR-OPN-16009847	-	The ORR and PFS rates were 90.5% and 83.3%, respectively, at a median follow-up of 24.3 months.	41
	Sequential CD19/22 CAR T cells following ASCT	ChiCTR-OPN-16009847	-	Median durable time of 14.03 months, and the ORR and CR rates were 81.81% and 54.55%, respectively.	42
Universal CAR T cells	CRISPR/Cas9 genome-edited universal CAR T cells	-	-	Two cases of r/r DLBCL in which patients received universal CAR T-cell therapy.	43

CAR: chimeric antigen receptor; ID: identity; Ref: reference; PFS: progression-free survival; CR: complete remission; r/r: relapsed/refractory; DLBCL: diffuse large B-cell lymphoma; PR: partial remission; SD: stable disease; B-ALL: B-cell acute lymphoblastic leukemia; CRi: complete remission with incomplete blood count recovery; ORR: overall response rate; OS: overall survival; PD-1: programmed death protein-1; MCL: mantle cell lymphoma; FL: follicular lymphoma; ASCT: autologous stem cell transplantation.

Table 5. Chimeric antigen receptor T-cell therapy in lymphoma: overview of current strategies to enhance safety.

Strategy	CAR T cells/object	Trial ID	Phase	Key findings	Ref.
Monitor	^{18}F-FDG PET/CT in predicting efficacy and adverse effects of CAR T-cell therapy	-	-	r/r NHL patients with higher baseline tumor burdens were found to have significantly increased CRS incidence and cytokine levels. The metabolic parameters including standardized uptake value, metabolic tumor volume and total lesion glycolysis were closely related to OS, PFS, and CRS in r/r NHL patients treated with CAR T cells.	44
Virus reactivation	Risk of HBV reactivation after CD19-CAR T-cell therapy	NCT02537977	-	r/r DLBCL patients with chronic HBV infection who receive CD19 CAR-T cell therapy are at risk of HBV reactivation, especially HBeAg-positive patients. Adequate antiviral prophylaxis is essential to prevent HBV reactivation in these patients.	45
	Humanized anti-CD19 CAR T-cell therapy in patients with chronic and resolved HBV infection	ChiCTR1800019622, ChiCTR1800018059	-	Among 15 patients with resolved HBV infection, 2 received antiviral prophylaxis, and the other 13 did not experience HBV reactivation without antiviral prophylaxis. One patient with resolved HBV infection experienced HBV reactivation 6 months after human CAR T-cell therapy and sequential allogeneic HSCT.	46
Infection	Incidence and risk factors associated with infection after CAR T-cell therapy	ChiCTR-ORN-16008948, ChiCTR-OIC-17011310, ChiCTR1800015575	-	The incidence of infection was 15.8% in the NHL cohort. An absolute neutrophil count <500 cells/mm^3 before CTI and infection during prior treatment were independent risk factors associated with a significantly increased infection density within 28 days after CTI. Similarly, corticosteroid treatment during CRS was an independent risk factor during days 29-180 after CTI.	47

CAR: chimeric antigen receptor; ID: identity; Ref: reference; ^{18}F-FDG: 18 fluoro-deoxyglucose; PET: positron emission tomography; CT: computed tomography; r/r: relapsed/refractory; NHL: non-Hodgkin lymphoma; CRS: cytokine release syndrome; OS: overall survival; PFS: progression-free survival; HBV: hepatitis B virus; DLBCL: diffuse large B-cell lymphoma; HSCT: hematopoietic stem cell transplantation; CTI: CAR T-cell infusion.

especially those with CD19-positive relapse from CAR T-cell therapy based on the FMC63 clone.[18]

The mechanism of developing an antigen-negative response is multifactorial in origin. As a consequence, the development of strategies to overcome antigen-negative relapse is complex. Recent studies have suggested that alternative targets (CD22, CD38)/combinations of multiple targets[11] might benefit ALL patients with antigen-negative response. However, Huang's group reported a retrospective comparison study of single CD19- and bi-specific CD19/CD22-targeted CAR T-cell therapy in patients with r/r ALL and suggested that the CR rate to the bi-specific treatment was comparable to the CR rate to the mono-specific treatment and did not reduce the recurrence rate in r/r ALL.[65] With respect to the diverse factors affecting the efficacy of CAR T cells, including the characteristics of the patients, the manufacturing process, and the infusion process of bi-specific products, more prospective studies are warranted in order to demonstrate that bi-specific CAR T cells could be an option to overcome antigen escape and delay the time of recurrence.

Given that severe adverse events may occur during CAR T-cell therapy, in particular those related to cytokine release, the management of these adverse events is very important. Tong *et al*. reported on the use of corticosteroids instead of tocilizumab as the first-line agent to manage cytokine release syndrome (CRS), and described that, even at high doses, corticosteroids did not undermine the efficacy of the CAR T cells, with regard to either proliferation or duration.[23] In addition, there was an exploratory attempt in one case to manage CRS, following the use of shRNA-IL6-modified CAR T cells, with suppression of *IL6* gene expression in the CAR T cells.[66]

Subjects with viral infection are usually excluded from clinical trials on CAR T cells, as elimination of B cells by anti-CD19 CAR T cells may lead to the reactivation of hepatitis B virus (HBV) and related hepatitis in the case of HBV infection. However, reports from Wen *et al*. and Li *et al*. indicated that HBV infection may not be an absolute contraindication to CAR T-cell therapy for r/r ALL patients if effective antiviral drugs are administered properly.[22,46]

Acute myeloid leukemia

Acute myeloid leukemia (AML) is an aggressive heterogeneous malignant disease of hematopoietic stem and progenitor cells and affects the blood and bone marrow. A wide variety of therapeutic strategies, including chemotherapy, immunotherapy and targeted therapy, has been

Table 6. Chimeric antigen receptor T-cell therapy in multiple myeloma: overview of current strategies to enhance efficacy.

Strategy	CAR T cells/object	Trial ID	Phase	Key findings	Ref.
Multi-target	A bi-specific CAR T-cell therapy targeting BCMA and CD38 (BM38 CAR T cells)	ChiCTR1800018143	I	Sixteen patients, including 10 (62.5%) with genetic abnormalities and 5 (31.25%) with extramedullary lesions, received BM38 CAR T cells. Fourteen (87.5%) patients achieved an overall response with 8 (50%) sCR, 2 (12.5%) VGPR and 4 (25.00%) PR. Fourteen (87.5%) achieved bone marrow MRD-negative status. PFS rate at 9 months was 75%.	48
	CD38 and BCMA bi-specific CAR T cells	ChiCTR1900026286	-	Of 16 evaluable patients, 14 (87.5%) responded to the treatment, including 13 with sCR and 1 with PR, while 2 patients did not respond. At a median follow-up of 11.5 months, of the 13 patients who achieved sCR, 76.9% (10/13) did not relapse or progress during follow-up.	49
	Anti-CD19 and anti-BCMA CAR T-cell sequential infusion followed by lenalidomide maintenance after ASCT	NCT 03455972	-	Ten high-risk newly diagnosed MM patients received treatment. The ORR was 100%: the best response being sCR (90%), and 10% had a CR.	50
CAR structure	Bi-epitopic CAR T-cell targeting BCMA (LCAR- B38M)	ChiCTR-ONH-17012285	I	Among 17 cases, the ORR was 88.2%, with 13 achieving sCR and 2 reaching VGPR, while 1 patient did not respond.	51
	Fully human BCMA-targeting CAR T cells (CT103A)	ChiCTR180001813 7	I	The ORR was 100%, with 72.2% of the patients achieving CR or sCR. Patients who relapse after prior murine BCMA CAR T-cell therapy may still benefit from CT103A.	52
	Humanized anti-BCMA CAR T cells	ChiCTR1800017051	-	Seven r/r MM patients with extramedullary disease and 13 without extramedullary disease received humanized anti-BCMA CAR T-cell therapy. The ORR in all the r/r MM patients was 80% (16/20). The CRS and ICANS grades were much higher in patients with extramedullary disease.	53
	BCMA-targeted fourth-generation CAR T cells secreting IL-7 and CCL19	NCT03778346	-	Preliminary results showed that 1 of 2 patients achieved CR and the other patient achieved VGPR of an extramedullary recurrence.	54

CAR: chimeric antigen receptor; ID: identity; Ref: reference; BCMA: B-cell maturation antigen; sCR: stringent complete remission; VGPR: very good partial remission; PR: partial remission; MRD: minimal residual disease; MM: multiple myeloma; CR: complete remission; ORR: overall response rate; r/r: relapsed/refractory; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

developed for AML. The prognosis and survival outcomes in AML patients after standard chemotherapy remain poor with estimated 5-year survival rates of 40-55% and 10-15% in patients <60 and >60 years old, respectively, making it imperative to develop new, targeted immunotherapies.[67] Selective elimination of cancerous cells is of the utmost importance in AML patients, because many myeloid antigens are also expressed on healthy hematopoietic stem and progenitor cells, leading to the destruction of the bone marrow and other toxic effects if non-selective agents are used. It is therefore crucial to find a suitable target for CAR T-cell treatment in AML. CD33 is known to be expressed highly in most AML patients thereby making it a potential target for the treatment of AML. In 2014 the first Chinese clinical study on autologous CD33-targeted CAR T-cell therapy in r/r AML patients was reported: a remarkable decrease in blasts in bone marrow was observed within 2 weeks after starting therapy and the adverse events were manageable.[68] Building on this, numerous tumor antigens, including

Table 7. Chimeric antigen receptor T-cell in multiple myeloma: overview of current strategies to enhance safety.

Strategy	CAR T cells/object	Trial ID	Phase	Key findings	Ref.
Monitor	ALC prior to LD affects outcomes in MM patients treated with CAR T cells	-	-	A better deep response rate was observed in patients with a high pre-LD ALC than in patients with a low pre-LD ALC (76% *vs.* 41%; *P*=0.002). Patients with a low pre-LD ALC had significantly inferior OS (median 15.4 months *vs.* not reached) and PFS (median PFS 8.4 *vs.* 27.3 months) compared with those with a high pre-LD ALC.	55
Virus reactivation	BCMA CAR T cells in MM patients co-infected with chronic HBV	-	-	Among 8 patients with MM who had resolved HBV infection, 2 given prophylactic anti-HBV drugs did not exhibit HBV reactivation. Further, 5/6 patients who did not receive prophylactic antiviral drugs, did not exhibit HBV reactivation, while 1 showed recurrence of HBsAg without detection of HBV DNA or damage to liver function. The ORR was 100%, and PFS at 12 months was 88.89%.	56
Immune reconstitution	Humoral immune reconstitution after anti-BCMA CAR T cells	ChiCTR-OIC-17011272	-	Anti-BCMA CAR T cells caused 7 months of aplasia of normal bone marrow plasma cells and a longer period of hypogammaglobulinemia, suggesting a profound and lasting humoral deficiency.	57
Renal impairment	Anti-mBCMA and/or anti-hsCD19 CAR T cells	ChiCTR-OIC-17011272	-	Combined anti-mBCMA with anti-hsCD19 CAR T cells or single anti-mBCMA CAR T-cell therapy is effective and well-tolerated in r/r MM patients with renal impairment and can restore renal function at high response rate.	58

CAR: chimeric antigen receptor; ID: identity; Ref: reference; ALC: absolute lymphocyte count; LD: lymphodepletion; MM: multiple myeloma; OS: overall survival; PFS: progression-free survival; HBV: hepatitis B virus; ORR: overall response rate; BCMA: B-cell maturation antigen; mBCMA: murine BCMA; r/r: relapsed/refractory; hsCD19: humanized CD19-specific.

CD38, CLL1, and CD123, have been explored as potential target antigens for AML treatment. Recently, CD38-targeted CAR T-cell therapy was tested as a new option in AML patients who relapsed following allogeneic HSCT. Qingya *et al*. conducted a prospective study to evaluate the efficacy and safety of CD38-targeted CAR T cells in such patients and reported that 4 weeks of infusion of CD38 CAR T cells led to CR in four of six (66.7%) patients, with median overall survival and leukemia-free survival times of 7.9 and 6.4 months, respectively. Furthermore, adverse events were clinically manageable in all six patients.[69]

CLL1 is highly expressed on AML stem cells, monocytes and blast cells but not on normal hematopoietic stem cells, thereby making it an actionable target in AML. Zhang *et al*. described that autologous anti-CLL1 CAR T-cell therapy in four children with r/r AML was efficacious; three of the children achieved CR and minimal residual disease negativity. Moreover, adverse events were low-grade and manageable in all the patients.[70] In addition, a recent comparative study by Kunlin *et al*. evidenced similar efficacy/safety profiles of 4-1BB and CD28/CD27-equipped CLL1-based CAR T cells in the treatment of children with r/r AML, with ORR of 67% and 75% in the two groups, respectively.[71]

Lymphoma

Lymphomas are systemic malignancies originating from lymphocytes. These heterogeneous lymphoid neoplasms can be classified into Hodgkin lymphomas and non-Hodgkin lymphomas (NHL). The incidence rates of Hodgkin lymphoma and NHL in China are ~0.46 and 4.29 cases per 100,000 persons, respectively.[72] In this review, we mainly discuss the development of CAR T-cell therapy in NHL because of the higher incidence of this form of lymphoma. The first-line treatment for NHL is chemoimmunotherapy with or without radiation. However, ~20-30% of patients eventually develop resistance, and the outcome of such patients is not entirely satisfactory, thereby warranting new approaches. CD19 is the most explored target of CAR T-cell therapy in lymphoma, and research has focused on both murine and fully human binding domains. Several CD19-targeted clinical studies have documented ORR ranging from 50% to 100% and CR rates from 20% to 66.7%.[7] Despite the significant efficacy of CD19 CAR T-cell therapy in NHL, 20-30% of cases relapse after this treatment because of antigen loss. Furthermore, given the heterogeneity of NHL, CD19 is not universally expressed on all lymphoma cells. The search for other targets is, therefore, very important. A robust pipeline of different targets for treating NHL, including B7-H3, Igβ, CD79b, CD30, BAFF,

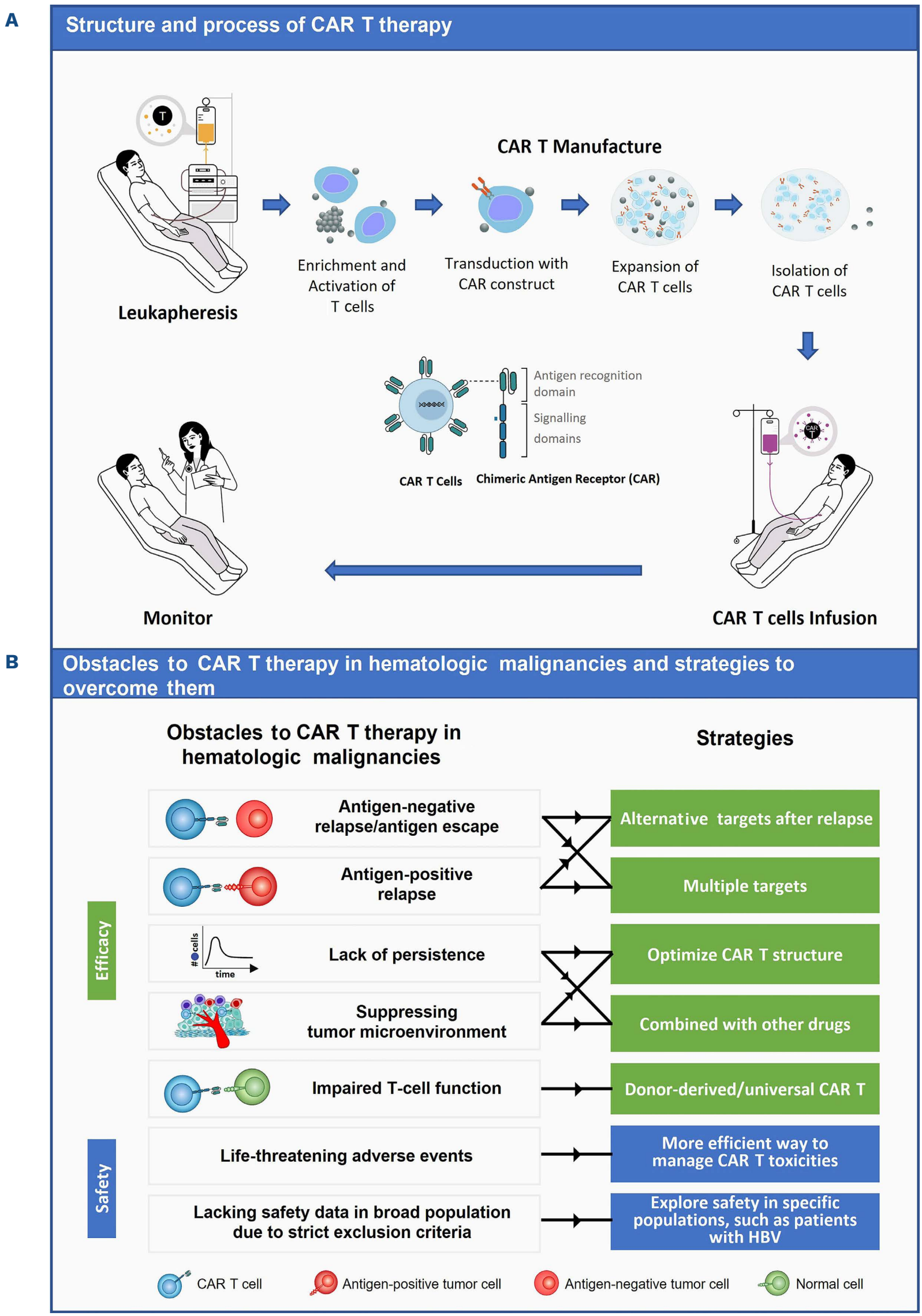


Figure 4. Chimeric antigen receptor T-cell therapy. (A) Structure and process of chimeric antigen receptor (CAR) T-cell therapy. (B) Obstacles to CAR T-cell therapy in hematologic malignancies and strategies to overcome them. HBV: Hepatitis B virus.

CTLA4, CD20 and CD70, is currently being explored and both pre-clinical and clinical studies are underway. Considering the significant efficacy of CD20 monoclonal antibody in NHL, CD20 was selected as one target and it is in the early exploratory stage. In 2014, Yao Wang *et al*. reported prolonged tumor regression following the use of CD20 CAR T cells in patients with DLBCL, and three of five evaluable patients with bulky tumor burden attained 3 to 6 months of tumor regression.[73]

Multi-target CAR T-cell therapy is an optimal strategy to overcome the immune escape of tumor cells. At present, the majority of studies have used CD19 in combination with other targets to construct multi-target CAR T cells, which simultaneously express multiple targets on the surface of the T cells. Lymphoma patients with high-risk factors, such as extra-nodal involvement, high-risk cytogenetics and limited response after salvage treatment are more prone to disease progression and may possibly benefit more from multi-target CAR T-cell therapy. Chen *et al*. reported that ten of 14 patients with r/r aggressive B-cell lymphoma with extra-nodal involvement who received sequential anti-CD22/anti-CD19 CAR T cells achieved objective responses, and seven of 14 achieved CR.[74] Jia *et al*. described that CD19/22 CAR T-cell cocktail therapy improved the long-term outcome of patients with r/r double-hit lymphoma.[27]

CAR T-cell therapy is a personalized immunotherapy and there are now a few potential therapeutic targets for the CAR T cells in lymphoma. As a result, the targets of the CAR T cells can be selected according to the patient's own characteristics. Cheng *et al*. reported a multi-CAR T-cell regimen for r/r B-cell lymphoma based on the patients' specific tumor antigen profile. The choice of CAR T-cell targets was determined by immunostaining tumor biopsies for CD19, CD22, CD30, GD2, and PSMA. Three of four patients achieved CR, and all of them have been in remission for >1 year.[75]

The mechanisms underlying relapse after CD19-targeted therapy are multifactorial and still poorly elucidated. A possible way to improve the efficacy of CAR T-cell therapy is to combine it with other treatment options. Cuicui *et al*. found that intensive debulking chemotherapy improved both short-term and long-term efficacy of anti-CD19 CAR T-cell therapy in r/r DLBCL with high tumor bulk.[76] Changju *et al*. reported that radiotherapy before CAR T-cell therapy in r/r DLBCL patients with high tumor burden produced a higher ORR (100%) and less severe CRS and neurotoxicity.[77]

In addition to traditional treatment, combined targeted therapy (BTK inhibitor/PD-1 blocker) and immunotherapy are also hot subjects for combination regimens.

Another strategy is to optimize the structure of the CAR T cells themselves. Inhibitory signals that CAR T cells encounter in the tumor microenvironment are often reported to impair the efficacy of CAR T-cell therapy. Xiaoqian *et al*. evaluated the efficacy of a novel dominant-negative PD-1-armored anti-CD19 CAR T cells in nine NHL patients and found an ORR of 77.8% (n=7/9) and a CR rate of 55.6% (n=5/9). In addition, the CAR T cells expanded after infusion and continued to be detectable at >12 months in patients with ongoing CR.[33] Similarly, Wenbin Qian *et al*. illustrated the efficacy of novel CD19-specific CAR T cells that express a PD-1/CD28 chimeric switch-receptor (CD19-PD-1/CD28-CAR) in r/r PD-L1-positive B-cell lymphoma and DLBCL patients who had relapsed after different CD19-directed CAR T-cell therapies.[35] There are also studies comparing the effect of different co-stimulatory domains on CAR T-cell efficacy and the control of CAR T-cell expansion, and apoptosis through suicide switches.[36]

Although autologous HSCT is the standard-of-care treatment for r/r lymphoma, studies are now suggesting that the clinical outcomes after CAR T-cell therapy are superior to those produced by autologous HSCT. The next step forward could be to combine CAR T cells and autologous HSCT. Indeed, Wang *et al*. described that the combination of autologous HSCT and anti-CD19 CAR T-cell therapy was beneficial in r/r DLBCL patients (n=14) who had a median progression-free survival of 14.82 months and an overall survival rate of 64.29%.[78]

Despite the aforementioned valuable options, several obstacles, such as the quality and quantity of T cells in intensive treatments, have limited the availability of autologous CAR T cells and their clinical usage. Recent studies have indicated the feasibility of using allogeneic universal CAR T cells in r/r lymphoma. Guo *et al*. reported two successful cases of treatment using CRISPR/Cas9 genome-edited universal CAR T cells negative for T-cell receptor and human leukocyte antigen class I molecules in patients with r/r lymphoma.[43]

CAR T-cell therapy is associated with unique adverse events, so appropriate methodology must be established to predict the occurrence and severity of such events. Jiasheng *et al*. conducted a retrospective study and showed that NHL patients with greater baseline disease burden were susceptible to more severe CRS, whereas patients with mild and moderate CRS (grade 0-2) had significantly lower metabolic tumor volume and total lesion glycolysis than those with severe CRS (grade 3/4).[79]

HBV reactivation is a well-recognized complication in lymphoma patients with concomitant viral infection. Wei *et al*. conducted a *post-hoc* analysis of two prospective clinical trials involving the use of CNCT19 CAR T cells (autologous second-generation anti-CD19 CAR T cells with 4-1BB as a co-stimulatory domain) in B-cell lymphoma patients and reported that anti-CD19 CAR T-cell therapy could be safely administered in B-cell lymphoma patients with concomitant HBV infection. However, antiviral prophylaxis was suggested for the patients treated with CNCT19 cells.[80]

Multiple myeloma

MM is characterized by uncontrolled proliferation of clonal plasma cells in bone marrow and accounts for 10% of blood cancers. It is associated with a mortality rate of 0.67 per 100,000 persons in China.[81] BCMA-targeted CAR T-cell therapy has achieved great success in MM, and two products have been approved by the FDA for MM patients who have received ≥4 lines of therapy, namely idecabtagene vicleucel and ciltacabtagene autoleucel (also named LCAR-B38M). The efficacy of different BCMA CAR T-cell therapies varies and there are other differences between the products. Pivotal studies demonstrated ORR and CR rates of 73% and 33%, respectively, for idecabtagene vicleucel[82] and 97% and 67%, respectively, for ciltacabtagene autoleucel.[83] Head-to-head comparisons of randomized controlled clinical studies are therefore now warranted. The long-term outcome of patients treated with idecabtagene vicleucel and ciltacabtagene autoleucel also varies considerably.

In addition to differences in study design and patients' characteristics, the inherent characteristics of different BCMA CAR T cells might affect their efficacy. Here we summarize the relevant studies on the modification and optimization of BCMA CAR T cells in China. The variable heavy chain domain of heavy-chain-only antibodies is the variable fragment of heavy-chain antibodies of camelidae and, like conventional antibodies, it is functional in antigen binding. It is a small, stable and single domain structure with high affinity and specificity comparable to those of single chain variable fragments (scFv). Lu *et al*. evaluated the efficacy of a single variable heavy chain domain of heavy-chain antibody-directed BCMA CAR T cells in r/r MM patients (n=34) and reported an ORR of 88.2% and stringent CR rate of 55.9%; the median progression-free survival was 12.1 months.[84] Wan-Hong Zhao *et al*. conducted a phase I study of LCAR-B38M, which is a dual epitope-binding CAR T- cell therapy directed against two distinct BCMA epitopes and documented an ORR of 88% (39/57 patients) and CR rate of 68% in r/r MM patients.[85] The long-term follow-up (median 19 months) results, presented at the 61st American Society of Hematology Annual Meeting in 2019, included a median progression-free survival of 20 months.[86]

Other strategies to optimize CAR T cells include humanization and arming. Duan *et al*. constructed BCMA-targeted fourth-generation CAR T cells expressing IL-7 and CCL19 for the purpose of enhancing the cells' expansion, differentiation, migration and cytotoxicity and demonstrated their efficacy in r/r MM patients. The preliminary results showed that one of two patients achieved a CR, and the other patient had a very good partial response of an extramedullary recurrence.[54]

Since the efficacy of CAR T cells targeting BCMA has been validated, CAR T cells targeting other antigens have been used in combinations with those targeting BCMA. One of the most common targets combinations is BCMA and CD19. B-lymphocyte antigen CD19, which is expressed by B cells prior to terminal differentiation into plasma cells, is associated with enhancement of myeloma tumor-propagating and drug-resistance properties. Zhiling Yan *et al*. conducted a phase II trial to evaluate the efficacy of a combination of humanized anti-CD19 (1×10^6 cells/kg) and anti-BCMA CAR T cells (1×10^6 cells/kg) in r/r MM patients (n=22) and reported an ORR of 95% including nine (43%) stringent CR, three (14%) CR, five (24%) very good partial responses, and three (14%) partial responses.[7] Using an alternative strategy, Lingzhi Yan *et al*. tested sequential CD19 and BCMA-specific CAR T-cell treatments in r/r MM. The patients received one dose of a CD19 CAR T-cell infusion on day 0 and thereafter a split-dose of BCMA CAR T-cell infusions over 2 days. The ORR was 90% (5 partial responses and 4 stringent CR).[88] Other targets combined with BCMA include CD38[49] and CS1, and both have been studied in MM, although these novel dual-targeted CAR T cells are mostly in preclinical development.

Renal impairment is a common complication of MM, but immunomodulatory agents and other treatments have been shown to be effective in patients with varying degrees of renal impairment. Shao-long *et al*. reported the efficacy of anti-BCMA CAR T-cell therapy in r/r MM patients with impaired renal function, with a median progression-free survival of 181 days and overall survival of 238 days, and further suggested that CAR T-cell therapy could be beneficial to renal function in r/r MM.[89]

Reactivation of HBV infection while undergoing anticancer therapy is an unwanted event in patients with chronic or resolved HBV infection. However, Han *et al*. described that BCMA CAR T-cell therapy could be administered safely and no HBV reactivation was observed among the nine r/r MM patients with resolved HBV infection.[56]

Ongoing challenges with chimeric antigen receptor T-cell therapy and future directions

As discussed, CAR T cells have become a major source of cellular immunotherapy for hematologic malignancies. In China, a number of CAR T-cell products are poised to launch a new therapeutic era. The main CAR T-cell trials are in the field of B-cell malignancies, such as lymphoma, leukemia and myeloma. Admittedly, CAR T-cell therapy is a complex process, and challenges occur throughout all parts of the exploratory work, including patient's recruitment and enrollment, the manufacturing process, delivery, the gap period between leukapheresis and infusion, in addition to the enormous cost, and so on. Despite higher ORR, relapse and resistance have been barriers limiting

the clinical feasibility of this therapy. It is to be hoped that innovative engineering can circumvent these barriers.[90,91] Another challenge that remains to be addressed adequately is the management of CRS and immune effector cell-associated neurotoxicity syndrome (ICANS), which are the most common toxicities related to CAR T-cell therapy.[92] Chinese researchers have actively explored a variety of cytokine inhibitors, based on drug accessibility, for the management of CRS. These include etanercept (a tumor necrosis factor-α inhibitor),[93] tocilizumab (an anti-IL-6 monoclonal antibody), and ruxolitinib (a JAK 1 and JAK2 inhibitor).[94] Vascular endothelial activation has been shown to contribute to the development of CRS and ICANS after CAR T-cell therapy. Therefore, blockade of tumor necrosis factor-α and interleukin-1β is also being investigated as a potential therapeutic target for the treatment of CAR T-cell therapy-associated CRS and ICANS.[95] Furthermore, Lu *et al*. have described a role for the pore-forming protein gasdermin E (GSDME) in release of pro-inflammatory cytokines during tumor cell pyroptosis leading to CRS and hence blockade of this pathway could be another potential strategy for the management of CRS.[96] The incidence of ICANS following CAR T-cell therapy appears to be significantly lower in the Chinese population than in the US population. For myeloma, the incidence of ICANS in BCMA CAR T-cell-treated Chinese r/r MM patients was 2.1%,[97] compared with 17% reported in the US population.[83] For lymphoma, neurotoxicity was reported in 87% of patients in the ZUMA-1 study conducted in the USA and Israel and the incidence of grade ≥3 adverse events was 31%.[98] In contrast, in the Chinese bridging study of axicabtagene ciloleucel, neurological toxicity occurred in 42% of patients and grade ≥3 adverse events were reported in 8% of patients. Understanding the mechanisms underlying these differences in ICANS between Chinese and American populations after CAR T-cell therapy would help in the development of better treatments and facilitate the prevention of these adverse events.

In China, the competition towards the commercial development of CAR T-cell therapy has intensified. However, consensus and guidelines regarding the targets and discrepancies between the efficacy of CAR T-cell products are challenging and urgently needed. Furthermore, the variable distribution of cell doses in the clinical trials conducted so far might reflect an insufficient exploration of cellular potency and pharmacodynamic characteristics of CAR T cells. Therefore, unified systematic management and operational guidance need to be implemented across hospitals/clinical study centers in order to promote the CAR T-cell industry.

Conclusions

CAR T-cell therapy is developing rapidly due to continuous scientific breakthroughs from CAR T cells targeting CD19 and BCMA, providing another pathway to improve the prognosis and quality of life of patients with hematologic malignancies. In contrast, CAR T-cell therapy has less impact on solid tumors. Admittedly, non-negligible issues, such as high cost, the time-consuming production process, inherent risks from manufacturing failures, immune-related adverse events, the problems of r/r disease, and inability to infiltrate solid tumor tissues, remain to be resolved, and are currently posing limits to the treatment of certain hematologic malignancies. It is now essential to develop products with acceptable cost and safety in order to extend the benefits of CAR T cells to a larger population.

Disclosures

No conflicts of interest to disclose.

Contributions

X-JH designed the review and wrote the manuscript. WS wrote the manuscript. AB-L and HH discussed and revised the manuscript. All authors gave final approval of the manuscript.

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Data-sharing statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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