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RAPID COMMUNICATION

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Clinical trials of CAR-T cells in China

Bingshan Liu^{1,2}, Yongping Song^{2*} and Delong Liu^{2*} 

Abstract

Novel immunotherapeutic agents targeting tumor-site microenvironment are revolutionizing cancer therapy. Chimeric antigen receptor (CAR)-engineered T cells are widely studied for cancer immunotherapy. CD19-specific CAR-T cells, tisagenlecleucel, have been recently approved for clinical application. Ongoing clinical trials are testing CAR designs directed at novel targets involved in hematological and solid malignancies. In addition to trials of single-target CAR-T cells, simultaneous and sequential CAR-T cells are being studied for clinical applications. Multi-target CAR-engineered T cells are also entering clinical trials. T cell receptor-engineered CAR-T and universal CAR-T cells represent new frontiers in CAR-T cell development. In this study, we analyzed the characteristics of CAR constructs and registered clinical trials of CAR-T cells in China and provided a quick glimpse of the landscape of CAR-T studies in China.

Background

Novel immunotherapeutic agents targeting CTLA-4, programmed cell death-1 protein receptor (PD-1), and the ligand PD-L1 are revolutionizing cancer therapy [1–7]. Cancer immunotherapy by re-igniting T cells through blocking PD-1 and PD-L1 is highly potent in a variety of malignancies [8–12]. Allogeneic hematopoietic stem cell transplantation has been proven to be a curative immunotherapy for leukemia though with significant toxicities [13–18]. Autologous T cells with re-engineered chimeric antigen receptors (CAR-T) have been successfully used for leukemia and lymphoma without graft-vs-host diseases [19–25]. The first such product, tisagenlecleucel, has recently been approved for clinical therapy of refractory B cell acute lymphoblastic lymphoma (ALL). More and more clinical trials of CAR-T cells are being done throughout the world [26–38].

In recent years, more and more clinical trials from China are being done and registered in ClinicalTrials.gov. CAR-T cells have become a major source of cellular immunotherapy in China. This study summarized the CAR-T clinical trials being conducted in China and provided a quick glimpse of the landscape of CAR-T studies in China.

Methods

We searched ClinicalTrials.gov using keywords “CAR T,” “CAR-T,” “chimeric antigen receptor,” “adoptive therapy,”

“third generation chimeric,” and “fourth generation chimeric”; country: China. All relevant trials registered at the ClinicalTrials.gov prior to July 18, 2017, were included in the analysis. One trial was excluded (NCT03121625) because the target antigen was not disclosed. A search of the PubMed database was also done to include those trials and cases that have been published.

Results

Distribution of CAR-T trials in China

Currently, there are 121 trials reported and/or registered at ClinicalTrials.gov from China (Table 1). The trials are mainly carried out in leading hospitals from Beijing, Shanghai, Guangzhou, and Chongqing. CAR-T trials are started in hospitals throughout China. In this study, to avoid duplication of trials that can lead to miscalculation, those trials in Chinese registries were not included. It is possible that the number of institutions carrying out CAR-T trials will increase at a slower pace once regulatory policies are in place. We believe these CAR-T cells should be regulated as drugs [39].

Chimeric antigen receptors, vectors, and co-stimulatory molecules used in the CAR constructs

T cell receptors (TCRs) are engineered by incorporating a specific antigen-targeting element and CD3 element to form a completely novel TCR structure, the chimeric antigen receptor (CAR) [35, 40]. In addition, several co-stimulating sequences have been used to facilitate the expansion of the CAR-T cells [41]. CAR-engineered T lymphocytes have been

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Table 1 Distribution of clinical trials with CAR-T cells in China

| | |
|-----------|----|
| Beijing | 30 |
| Shanghai | 22 |
| Guangdong | 20 |
| Chongqing | 15 |
| Jiangsu | 13 |
| Others | 21 |

in active clinical development to treat patients with advanced leukemia, lymphoma, and solid tumors [42–45].

One of the major hurdles in CAR-targeted cellular therapy has been the limited cell dose due to the lack of adequate *in vivo* cell expansion. Co-stimulatory signals can enhance immune responses of effector T cells [46]. Inducible co-stimulatory signal (ICOS), 4-1BB (CD137), CD28, OX40 (CD134), CD27, and DAP10, along with CD3 ζ , have been investigated [31, 47–50]. Among these, 4-1BB (CD137), CD28, and CD3 ζ are the most commonly used COS elements in the CARs (Tables 2, 3, and 4) [51, 52].

Most CARs in the CAR-T trials in China are second-generation CAR constructs, which have one co-stimulatory signal [41]. A trial of CAR-T cells containing a third-generation CAR construct with both CD28 and CD137 co-stimulatory signals is still recruiting patients with relapsed/refractory ALL (NCT02186860). Fourth-generation CARs have incorporated additional elements in the CAR constructs, such as an inducible caspase-9 gene element that can lead to self-destruction by apoptosis of the CAR-T cells [53]. A total of 10 trials of CAR-T cells contain a fourth-generation CAR (Table 5). Among these, five trials are evaluating CARs with an inducible caspase-9 suicide switch.

The recombinant CAR cassette is typically packaged into a pseudo-lentivirus vector which can efficiently incorporate into the genome of T cells. To date, the lentiviral vector is the most commonly used vector in CAR-T cells. The other vector commonly used is the retroviral vector (Tables 2, 3, and 4).

Antigen targets

By altering a specific antigen-targeting element, the specificity of the CAR-T cells can be easily re-directed to a specific type of malignancy. This makes the CAR-T cell therapy highly versatile. A number of antigens have been targeted in this way. More and more antigens are being engineered into CAR-T cells, leading to a large repertoire of CAR-T cells that are being explored for the therapy of both solid and hematological malignancies (Tables 3 and 4).

CD19 is the most commonly targeted antigen to date (Table 2). Out of the 121 trials, 57 trials have CD19 as a target. Currently, there are 19 clinical trials in China targeting non-CD19 antigens, including CD20, CD22, CD30, CD33, CD38, CD123, CD138, BCMA, and Lewis Y antigen for hematological malignancies (Table 3). Dual-

and multi-specificity CAR-T cells have also been in clinical trials in China.

Current trials on hematological malignancies

The most common type of diseases in CAR-T trials are B cell malignancies, including leukemia, lymphoma, and myeloma.

The CD19-targeted autologous CAR-T product, tisa-genlecleucel, was recently approved by FDA for therapy of refractory/relapsed (r/r) B cell ALL. In 30 patients including children and adults who received this product, 90% of them achieved complete remission (CR) [54]. Severe cytokine-release syndrome (CRS) was reported in 27% of the patients. This product has been in clinical trials for CD19+ B cell malignancies, including CLL, ALL, and lymphoma [21–24, 54, 55]. In a Chinese study (NCT 02813837), 30 patients (5 children and 25 adults) with r/r ALL were treated with autologous CD-19 CAR-T cells [56]. In this 2017 report of preliminary results of a seven-center clinical trial, CR was 86% and severe CRS was seen in 26% of the patients [56]. Successful outcome has been reported with other CAR-T cells against CD19 antigen in r/r ALL [29, 32, 57–59].

The CD19-specific CAR-T cells, axicabtagene ciloleucel (axi-cel, KTE-C19), have been reported to be safe for treatment of aggressive lymphomas including r/r diffuse large cell lymphoma (DLBCL) [25]. In the phase II part of the ZUMA-1 trial, overall response rate (ORR) was 76% (47% CR and 29% PR) at the time of report in the cohort 1 of 51 patients [60]. This product is currently under evaluation by FDA.

CD33 and CD123 are targets on myeloid leukemias. Currently, there are three trials on CAR-T cells targeting CD33 and two trials targeting CD123 antigen in China (Table 3). In the USA, three CAR-T trials targeting CD123 were either terminated (NCT02623582) or suspended (UCART123, NCT02159495, and NCT03190278) at this time.

B cell maturation antigen (BCMA) is an antigen target on myeloma cells. Currently, three trials on BCMA-targeted CAR-T cells are being done in r/r myeloma in China (Table 3). In one of the trials of CAR-T cells targeting BCMA in China, 19 patients with r/r multiple myeloma were evaluable and 7 of the patients were followed for more than 6 months at the time of the report [61]. CRS was observed in 14 (74%) patients. The ORRs were close to 100% in the evaluable r/r myeloma patients. The outcome from the preliminary report was highly encouraging. Complete response was also reported in a case of r/r myeloma patient who received autologous CTL019 cells, even though 99.95% of the myeloma cells were negative for CD19 [38, 62]. It appears therefore that multiple myeloma is highly sensitive to immunotherapy.

Table 2 Clinical trials of CD19-directed CAR-T cells in China

| Target antigen | Diseases | CAR | Vector | NCT no. |
|----------------|--|---------------------------------------|----------|-------------|
| CD19 | Leukemia, lymphoma | 4-1BB- CD3 ζ | RV | NCT01864889 |
| CD19 | B cell malignancies | CD28, CD137, CD27 | LV | NCT03050190 |
| CD19 | MCL | 4-1BB-CD3 ζ | RV | NCT02081937 |
| CD19 | Leukemia | NA | NA | NCT03142646 |
| CD19 | B cell lymphomas | CD27-CD3 ζ | LV | NCT02247609 |
| CD19 | Leukemia, lymphoma | NA | NA | NCT02349698 |
| CD19 | Elderly relapsed/refractory B cell ALL | NA | NA | NCT02799550 |
| CD19 | Leukemia, lymphoma | NA | NA | NCT02537977 |
| CD19 | B cell leukemia | NA | NA | NCT02644655 |
| CD19 | B cell leukemia and lymphoma | NA | NA | NCT02813837 |
| CD19 | B cell lymphoma | NA | NA | NCT02547948 |
| CD19 | B cell lymphoma | CD28-CD3 ζ | RV | NCT02652910 |
| CD19 | Leukemia, lymphoma | CD28, CD3 ζ | LV or RV | NCT02456350 |
| CD19 | Recurrent or refractory acute non-T-lymphocyte leukemia | NA | NA | NCT02735291 |
| CD19 | Lymphoma | NA | NA | NCT02728882 |
| CD19 | Leukemia, lymphoma | NA | NA | NCT02546739 |
| CD19 | B cell lymphomas | NA | NA | NCT02842138 |
| CD19 | ALL | NA | NA | NCT02810223 |
| CD19 | ALL | CD28-CD137-CD3 ζ | LV | NCT02186860 |
| CD19 | B cell leukemia, B cell lymphoma | CD3 ζ , CD28, and 4-1BB | LV | NCT02963038 |
| CD19 | NHL | TCR ζ , 4-1BB | LV | NCT03029338 |
| CD19 | B cell ALL | TCR ζ , 4-1BB | LV | NCT02975687 |
| CD19 | B cell leukemia and lymphoma | NA | LV | NCT02933775 |
| CD19 | B cell leukemia | 4-1BB | LV | NCT02672501 |
| CD19 | Central nervous system B cell acute lymphocytic leukemia | NA | NA | NCT03064269 |
| CD19 | ALL | 4-1BB | LV | NCT02965092 |
| CD19 | Acute leukemia | NA | NA | NCT02822326 |
| CD19 | Leukemia, lymphoma | CD28 or 4-1BB and a CD3 ζ | LV or RV | NCT03076437 |
| CD19 | Leukemia and lymphoma | NA | NA | NCT02851589 |
| CD19 | Leukemia and lymphoma | NA | NA | NCT02819583 |
| CD19 | DLBCL | NA | LV | NCT02976857 |
| CD19 | Recurrent or refractory B cell malignancy | NA | NA | NCT02782351 |
| CD19 | Leukemia and lymphoma | TCR ζ -CD28, TCR ζ -CD137 | NA | NCT02685670 |
| CD19 | B cell lymphoma | 4-1BB, CD3 ζ | NA | NCT03101709 |
| CD19 | ALL | NA | NA | NCT02924753 |
| CD19 | ALL | NA | NA | NCT03027739 |
| CD19 | B cell leukemia | NA | LV | NCT02968472 |
| CD19 | B cell lymphoma | CD28 ζ | NA | NCT02992834 |
| CD19 | AML | NA | NA | NCT03018093 |
| CD19 | Systemic lupus erythematosus | 4-1BB | LV | NCT03030976 |
| CD19 | NHL | NA | LV | NCT03154775 |
| CD19 | Lymphoma | NA | NA | NCT03086954 |

Table 2 Clinical trials of CD19-directed CAR-T cells in China (Continued)

| Target antigen | Diseases | CAR | Vector | NCT no. |
|-------------------------------|--|---------------------------------|--------|-------------|
| CD19 | ALL, CLL, lymphoma | CD28 or 4-1BB and CD3 ζ | NA | NCT03191773 |
| CD19 | B cell lymphoma | 4-1BB-CD28-CD3 | NA | NCT03146533 |
| CD19 | Leukemia | NA | NA | NCT03173417 |
| CD19 | Relapsed or refractory B cell lymphoma | 4-1BB | LV | NCT03208556 |
| CD19 | B cell leukemia and lymphoma | | | NCT03166878 |
| CD19 | B cell lymphoma | NA | NA | NCT03118180 |
| CD19 or CD20 | Relapse/refractory B cell malignancies | NA | LV | NCT02846584 |
| CD19 and CD20 | DLBCL | NA | NA | NCT02737085 |
| CD19 and CD22 | Hematopoietic/lymphoid cancer | TCR ζ , 4-1BB | NA | NCT02903810 |
| CD19/CD20 | B cell leukemia and lymphoma | CD3 ζ , 4-1BB-CD3 ζ | RV | NCT03097770 |
| CD19/CD22 | B cell malignancy | NA | RV | NCT03185494 |
| CD19/CD22 | B cell leukemia, B cell lymphoma | NA | LV | NCT03098355 |
| CD19/CD20/CD22/CD30 | B-NHL | NA | NA | NCT03196830 |
| CD19/CD20 | B cell malignancy | NA | NA | NCT03207178 |
| CD19 and CD20/CD22/CD38/CD123 | B cell malignancy | NA | LV | NCT03125577 |

AMMS Academy Military Medical Sciences, ALL acute lymphoblastic leukemia, AML acute myeloid leukemia, BCMA B cell maturation antigen, CTX cyclophosphamide, DLBCL diffuse large B cell lymphoma, FLU fludarabine, HL Hodgkin's lymphoma, LV lentiviral, MCL mantle cell lymphoma, NA not available, NHL non-Hodgkin lymphoma, RV retroviral, TCM traditional Chinese medicine

Table 3 Clinical trials of CAR-T cells targeting non-CD19 antigens in China

| Target Antigen | Disease | CAR | Vector | NCT no. |
|----------------|---|----------------------|--------|-------------|
| CD20 | Lymphoma | 4-1BB-CD3 ζ | LV | NCT01735604 |
| CD20 | B cell lymphoma | CD3 ζ and CD28 | RV | NCT02965157 |
| CD20 | B cell malignancies | NA | NA | NCT02710149 |
| CD22 | CD19-refractory or resistant lymphoma | TCR ζ , 4-1BB | RV | NCT02721407 |
| CD22 | Recurrent or refractory B cell malignancy | NA | NA | NCT02794961 |
| CD22 | B cell malignancies | NA | NA | NCT02935153 |
| CD30 | Lymphoma | NA | LV | NCT02274584 |
| CD30 | HL, NHL | NA | NA | NCT02259556 |
| CD30 | Lymphocyte malignancies | NA | NA | NCT02958410 |
| CD33 | AML | 4-1BB-CD3 ζ | RV | NCT01864902 |
| CD33 | AML | NA | NA | NCT02799680 |
| CD33 | Myeloid malignancies | NA | NA | NCT02958397 |
| BCMA | B cell malignancies | NA | NA | NCT02954445 |
| BCMA | Multiple myeloma | TCR ζ , 4-1-BB | RV | NCT03093168 |
| CD123 | Leukemia | NA | NA | NCT02937103 |
| CD123 | AML recurred after allo-HSCT | 41BB-CD3 ζ | NA | NCT03114670 |
| CD138 | Multiple myeloma | 4-1BB-CD3 ζ | RV | NCT01886976 |
| CD138/BCMA | Multiple myeloma | NA | NA | NCT03196414 |
| Lewis-Y | Myeloid malignancies | NA | NA | NCT02958384 |

AMMS Academy of Military Medical Sciences, ALL acute lymphoblastic leukemia, AML acute myeloid leukemia, BCMA B cell maturation antigen, CTX cyclophosphamide, FLU fludarabine, HL Hodgkin's lymphoma, LV lentiviral, MCL mantle cell lymphoma, NA not available, NHL non-Hodgkin lymphoma, RV retroviral, TCM traditional Chinese medicine

Table 4 Clinical trials of CAR-T cells for solid tumors in China

| Target antigens | Diseases | CAR | Vector | NCT no. |
|-----------------------|---|---------------------------------|--------|-------------|
| GPC3 | Hepatocellular carcinoma | NA | NA | NCT02723942 |
| GPC3 | Hepatocellular carcinoma | CD3 ζ , CD28, and 4-1BB | NA | NCT02395250 |
| GPC3 | Lung squamous cell carcinoma | NA | LV | NCT02876978 |
| GPC3 | Hepatocellular carcinoma and liver metastases | 4-1BB | NA | NCT02715362 |
| GPC3 | Hepatocellular carcinoma | 4-1BB | NA | NCT03130712 |
| GPC3 | Advanced hepatocellular carcinoma | 4-1BB-CD3 ζ | RV | NCT03084380 |
| GPC3 | Hepatocellular carcinoma, squamous cell lung cancer | NA | NA | NCT03198546 |
| GPC3 | Hepatocellular carcinoma | NA | LV | NCT03146234 |
| GPC3, mesothelin, CEA | Hepatocellular, pancreatic cancer, colorectal cancer | NA | LV | NCT02959151 |
| Mesothelin | Malignant mesothelioma, pancreatic Cancer, ovarian tumor, triple-negative breast cancer, endometrial cancer, other mesothelin-positive tumors | 4-1BB-CD3 ζ | RV | NCT02580747 |
| Mesothelin | Recurrent or metastatic malignant tumors | NA | NA | NCT02930993 |
| Mesothelin | Pancreatic cancer and pancreatic ductal adenocarcinoma | 4-1BB | NA | NCT02706782 |
| Mesothelin | Solid tumor, adult advanced cancer | NA | NA | NCT03030001 |
| Mesothelin | Advanced solid tumor | NA | NA | NCT03182803 |
| EpCAM | Liver neoplasms | NA | NA | NCT02729493 |
| EpCAM | Stomach neoplasms | NA | NA | NCT02725125 |
| EpCAM | Nasopharyngeal carcinoma and breast cancer | NA | LV | NCT02915445 |
| EpCAM | Colon cancer, esophageal carcinoma, pancreatic cancer, prostate cancer, gastric cancer, hepatic carcinoma | CD3 ζ , CD28 | LV | NCT03013712 |
| GD2 | Neuroblastoma | NA | LV | NCT02765243 |
| GD2 | Relapsed or refractory neuroblastoma | NA | NA | NCT02919046 |
| GD2 | Solid tumor | NA | LV | NCT02992210 |
| HER-2 | Advanced HER-2-positive solid tumors | CD3 ζ , 4-1BB-CD3 ζ | NA | NCT01935843 |
| HER-2 | Breast cancer | CD28-CD3 ζ | RV | NCT02547961 |
| HER-2 | Breast cancer, ovarian cancer, lung cancer, gastric cancer, glioma, pancreatic cancer | NA | NA | NCT02713984 |
| EGFR | Advanced EGFR-positive solid tumors | 4-1BB-CD3 ζ | LV | NCT01869166 |
| EGFR | Advanced solid tumor | NA | NA | NCT03182816 |
| EGFR | Colorectal cancer | 4-1BB-CD28-CD3 | NA | NCT03152435 |
| EGFRvIII | Recurrent glioblastoma multiform | NA | LV | NCT02844062 |
| EGFRvIII | Glioblastoma multiform | NA | NA | NCT03170141 |
| MUC1 | Malignant glioma of brain, colorectal carcinoma, gastric carcinoma | NA | NA | NCT02617134 |
| MUC1 | Advanced refractory solid tumor (hepatocellular carcinoma, NSCLC, pancreatic carcinoma, triple-negative invasive breast carcinoma) | CD28-4-1BB- CD3 ζ | LV | NCT02587689 |
| MUC1 | Advanced solid tumor | NA | NA | NCT03179007 |
| CEA | Lung cancer, colorectal cancer, gastric cancer, breast cancer, pancreatic cancer | NA | NA | NCT02349724 |
| EphA2 | EphA2-positive malignant glioma | NA | NA | NCT02575261 |
| LMP1 | Nasopharyngeal neoplasms | NA | NA | NCT02980315 |
| MG7 | Liver metastases | 4-1BB | NA | NCT02862704 |
| CD133 | Liver cancer, pancreatic cancer, brain tumor, breast cancer, ovarian tumor, colorectal cancer, ALL, AML | CD3 ζ , 4-1BB-CD3 ζ | RV | NCT02541370 |
| HerinCAR-PD1 | Advanced malignancies | NA | NA | NCT02873390 |

Table 4 Clinical trials of CAR-T cells for solid tumors in China (Continued)

| Target antigens | Diseases | CAR | Vector | NCT no. |
|-------------------------|--|-----|--------|-------------|
| HerinCAR-PD1 | Advanced solid tumor (lung, liver, and stomach) | NA | NA | NCT02862028 |
| PD-L1 CSR | Glioblastoma multiform | NA | NA | NCT02937844 |
| NY-ESO-1 | Advanced NSCLC | NA | LV | NCT03029273 |
| Zeushield | NSCLC | NA | NA | NCT03060343 |
| PSCA/MUC1/PD-L1/CD80/86 | Advanced lung or other cancers | NA | NA | NCT03198052 |
| PSMA, FRa | Bladder cancer, urothelial carcinoma bladder | NA | NA | NCT03185468 |
| Claudin18.2 | Advanced gastric adenocarcinoma, pancreatic adenocarcinoma | NA | LV | NCT03159819 |

CTX cyclophosphamide, FLU fludarabine, LV lentiviral, NA not available, NSCLC non-small cell lung cancer, RV retroviral

There are also a few registered clinical trials that are testing two or more CARs either simultaneously or sequentially. In the trial NCT02846584, patients receive intravenously infused autologous anti-CD19 or anti-CD20 CAR-T cells to treat B cell malignancies. Another trial, NCT02737085, is to explore the sequential therapeutic effect of anti-CD19 and anti-CD20 CAR-T cells in the treatment of DLBCL.

The trial NCT02903810 was planned with a treatment scheme of infusion of equal numbers of anti-CD19 and anti-CD22 CAR-T cells in the treatment of refractory hematologic malignancies. Two trials (NCT03097770 and NCT03098355) target two antigens simultaneously with one CAR construct (Table 2). These trials are ongoing at this time.

Current trials on solid tumors

Multiple solid tumors are being studied in CAR-T clinical trials. At the time of this report, 20 different antigens are being targeted in solid tumor trials (Table 4). GPC3, mesothelin, epidermal growth factor receptor (EGFR), and EpCAM were the most targeted antigens (Table 4). This is consistent with reports from international

trials [63–68]. Liver cancer remains the most commonly studied solid tumor in China [69]. In a preliminary report of a trial of CAR-T cells against CD133+ epithelial tumors (NCT02541370), 24 patients were enrolled, including 14 patients with sorafenib-refractory hepatocellular carcinoma (HCC), 7 with pancreatic carcinomas, 2 with colorectal carcinomas, and 1 with cholangiocarcinoma [69]. The number of CAR-T cells was found to be inversely related to the CD133+ epithelial cells in peripheral blood. There was a separate report treating refractory cholangiocarcinoma with sequential infusion of two different types of CAR-T cells targeting EGFR and CD133 [70].

Two trials in China are evaluating GD2 antigen-targeted CAR-T cells in neuroblastoma (Table 4). Another two trials are evaluating CAR-T cells against EGFRvIII+ glioblastoma. There was one case report in the literature on rapidly progressing refractory glioblastoma that showed dramatic CR to IL13R α 2-targeted CAR-T cells after repeated infusion [71]. In a separate report, nine patients with refractory EGFRvIII+ glioblastoma received autologous CART-EGFRvIII cells in a pilot study [66]. Interestingly, there was no CRS observed. CAR-T cell infiltration was shown in the resected tumor

Table 5 Clinical trials of CAR-T cells with fourth-generation CARs in China

| Target antigen | Disease | Vector | NCT no. |
|-------------------------------|--|--------|-------------|
| CD19 | B cell malignancies | LV | NCT03050190 |
| CD19 | B cell lymphomas | LV | NCT02247609 |
| CD19 | B cell leukemia | LV | NCT02968472 |
| CD19/CD22 | B cell leukemia, B cell lymphoma | LV | NCT03098355 |
| CD19 and CD20/CD22/CD38/CD123 | B cell malignancy | LV | NCT03125577 |
| CD30 | Lymphoma | LV | NCT02274584 |
| PSMA, FRa | Bladder cancer, urothelial carcinoma bladder | NA | NCT03185468 |
| EGFRvIII | Glioblastoma multiform | NA | NCT03170141 |
| GD2 | Neuroblastoma | LV | NCT02765243 |
| GD2 | Solid tumor | LV | NCT02992210 |

LV lentiviral vector, NA not available

specimen. This study suggested that the CAR-T cells are safe and immunologically active with tracking capability to the cancer cells in the brain.

Multiple antigens are being explored as targets in solid tumors for CAR-T cells (Table 4). Preliminary reports have been presented and published throughout the world [64, 65, 67, 72]. Outcomes from larger sample size and longer follow-up are clearly needed from these trials.

CAR-T trials for non-malignant diseases

There is currently one clinical trial of autologous CAR-T19 cells for patients with systemic lupus erythematosus (NCT03030976, Table 2). This trial is designed to infuse 1×10^6 cells/kg. More trials are expected to come for non-malignant diseases.

Discussion

This study analyzed CAR-T trials in China. Most CAR-T trials are employing autologous T cells. CD19 is the most commonly targeted antigen. Therefore, B cell leukemia and lymphoma are the most common malignancies in CAR-T trials. Solid tumors remain a significant challenge for CAR-T therapy [45, 70, 73, 74]. Challenges include selection of target antigens, management of toxicities, and modulation of tumor microenvironment [75, 76]. Loss of CD19 expression is a known mechanism for relapse from CD19-directed CAR-T therapy [77]. The first CAR-T product, tisagenlecleucel, was recently approved. KTE-C19 for large cell lymphoma is under evaluation by FDA [25, 60]. It is unclear which product among many ongoing clinical CAR-T trials in China has independent patent that may lead to final approval for clinical application in China.

It has been well documented that CAR-T cells can cross the blood-brain barrier [23, 78, 79]. CAR-T cells may become an effective therapy for refractory CNS diseases [66, 71, 78–81]. In addition to trials of single-target CAR-T cells, simultaneous and sequential CAR-T cells are being studied for clinical applications [70]. Multi-target CAR-engineered T cells are also entering clinical trials (Tables 2, 3, and 4).

The currently approved tisagenlecleucel CAR-T therapy relies on transduction of autologous T cells from patients. It is important therefore to be able to reliably obtain and propagate adequate amount of T cells. This may become a major limitation for wide application of this new therapy. Therefore, newer CARs are being actively investigated [41, 82–84]. Universal CAR-Ts have been generated by inactivating HLA class I molecules and used successfully in patients [82, 85, 86]. Allogeneic CAR-T cells are entering clinical trials [42, 87]. T cell receptor-engineered CAR-T cells represent another frontier in CAR-T cell development [88–90]. It is foreseeable that CAR-T immunotherapy will become a major modality of cancer therapy (Table 5) [91].

Abbreviations

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; BCMA: B cell maturation antigen; CTX: Cyclophosphamide; DLBCL: Diffuse large B cell lymphoma; FLU: Fludarabine; HL: Hodgkin's lymphoma; LV: Lentiviral; MCL: Mantle cell lymphoma; NHL: Non-Hodgkin lymphoma

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Availability of data and materials

The material supporting the conclusion of this study has been included within the article.

Authors' contributions

DL designed the study. All authors drafted the manuscript. All authors read and approved final manuscript.

Ethics approval and consent to participate

This is not applicable for this study.

Consent for publication

This is not applicable for this study.

Competing interests

The authors declare that they have no competing interests.

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