Adverse effects in hematologic malignancies treated with chimeric antigen receptor (CAR) T cell therapy: a systematic review and Meta-analysis

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Abstract

Background: Recently, chimeric antigen receptor-modified (CAR) T cell therapy for hematological malignancies has shown clinical efficacy. Hundreds of clinical trials have been registered and lots of studies have shown hematologic toxic effects were very common. The main purpose of this review is to systematically analyze hematologic toxicity in hematologic malignancies treated with CAR-T cell therapy.

Methods: We searched databases including PubMed, Web of Science, Embase and Cochrane up to January 2021. For safety analysis of overall hematologic toxicity, the rate of neutrophil, thrombocytopenia and anemia were calculated. Subgroup analysis was performed for age, pathological type, target antigen, co-stimulatory molecule, history of hematopoietic stem cell transplantation (HSCT) and prior therapy lines. The incidence rate of aspartate transferase (AST) increased, alanine transaminase (ALT) increased, serum creatine increased, APTT prolonged and fibrinogen decreased were also calculated.

Results: Overall, 52 studies involving 2004 patients were included in this meta-analysis. The incidence of any grade neutropenia, thrombocytopenia and anemia was 80% (95% CI: 68–89%), 61% (95% CI: 49–73%), and 68% (95%CI: 54–80%) respectively. The incidences of grade ≥ 3 neutropenia, thrombocytopenia and anemia were 60% (95% CI: 49–70%), 33% (95% CI: 27–40%), and 32% (95%CI: 25–40%) respectively. According to subgroup analysis and the corresponding Z test, hematological toxicity was more frequent in younger patients, in patients with ≥ 4 median lines of prior therapy and in anti-CD19 cases. The subgroup analysis of CD19 CAR-T cell constructs showed that 41BB resulted in less hematological toxicity than CD28.

Conclusion: CAR-T cell therapy has dramatical efficacy in hematological malignancies, but the relevant adverse effects remain its obstacle. The most common ≥ 3 grade side effect is hematological toxicity, and some cases die from infections or severe hemorrhage in early period. In long-term follow-up, hematological toxicity is less life-threatening generally and most suffered patients recover to adequate levels after 3 months. To prevent life-threatening infections or bleeding events, clinicians should pay attention to intervention of hematological toxicity in the early process of CAR-T cell therapy.

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**Background**

Hematological malignancies accounted for 1.2 million, that was around 7%, newly diagnosed cancer cases every year worldwide [1]. Among them, lymphocytic leukemia, lymphoma and multiple myeloma (MM) represent a large part. Chemotherapy, as a traditional and common treatment for them, is being replaced gradually by some novel therapies, like chimeric antigen receptor-modified (CAR-T) cell therapy.

CAR-T cells are produced strictly ex-vivo and then infused to patients by intravenous injection. The CARs, recognizing their targets by a specific mechanism distinct from classic TCRs, are comprised of an antigen-specific single-chain variable fragment (scFv) that is fused to an internal T-cell signaling domain and costimulatory molecules like CD28 or 41BB [2]. The development of CAR-T cell therapy was a wave of optimism for selected hematological malignancies in the past decades. Meanwhile, cytokine release triggered by CAR-T cell activation, expansion and cytotoxicity, leads to CRS, immune effector cell-associated neurotoxicity syndrome (ICANS) and even hematological toxicities [3, 4]. Adverse effects related to CAR-T cell therapy should be paid attention to, and there are already some reviews reporting the overall rate of CRS and ICANS. And hematological toxicity is the most common grade $\geq 3$ AE in CAR-T cell therapy [5]. Given that hepatotoxicity, nephrotoxicity and coagulation disorders are not rare in the treatment of hematological malignancies, we analyzed these incidences as the secondary outcome. The analysis of the landscape of hematological toxic effects associated with CAR-T cell therapy seems to be extremely significant.

We searched databases including PubMed and Web of Science to explore the adverse effects during the CAR-T cell therapy, and 52 studies involving 2004 patients were included in this meta-analysis. We mainly analyzed hematological toxicity, and we also conducted subgroup analysis. We aimed to provide some references for CAR-T cell therapy and draw clinicians’ attention to AEs associated with CAR-T cell therapy, besides CRS and neurotoxicity.

**Materials and methods**

This study is registered in International Prospective Register of Systematic Reviews (PROSPERO) and the number is CRD 42021237114. We did our meta-analysis and systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [6] and the checklist is shown in Supplementary Material.

**Search strategy**

We searched PubMed, Web of Science, Embase and Cochrane up to January 2021, and the terms for the literature search were “chimeric antigen receptor”, “CAR-T”, “chimeric antigen receptor-modified T cell therapy”, “blood system toxicity”, “hematopoietic system toxicity”, “hematological toxicity”, “adverse effects”, “side effects”, “leukemia”, “multiple myeloma”, “lymphoma” and “hematological malignancies”. To guarantee comprehensive search and to include all potentially relevant studies, we examined related meta-analysis and cross-referenced the references of identified articles. The search results were imported in Endnote X9 and duplicates were identified and removed through Endnote X9 and manually. Two independent researchers (Luo WJ and Mei H) screened retrieved documents and assessed independently full texts of articles on the basis of prespecified inclusion criteria. All disagreements were resolved by discussion with the third researcher (Hu Y).

**Selection criteria**

**Inclusion criteria**

We included both articles published in journal and abstracts from conference proceedings, which reported the incidence rate of hematological toxicity in patients with CAR-T cell therapy. Both single-arm trials and retrospective studies were included. Case-series with detailed information of treatment and outcome were also included. We analyzed the most recently updated results of each included clinical trial, whether reported in published articles or conference proceedings.

**Exclusion criteria**

We excluded studies published in languages other than English and Chinese, and those focusing on the efficacy or safety of combinations of CAR-T cell therapy and other therapies. Studies with insufficient data where our aimed AEs were not reported, irrelevant studies, and studies with two or fewer patients were excluded. Studies with the same NCT number were screened, and we excluded these reports with the shorter follow-up. Meanwhile, clinical guidelines, consensus documents and systematic reviews were excluded from our meta-analysis.
Data extraction

Two investigators independently reviewed and extracted the following information: study characteristics (first author, publication year, the number of included patients, ClinicalTrials.gov number, research design and the selected AEs criteria), patients characteristics (gender, age, pathological type, previous HSCT and prior therapy lines), intervention (pre-infusion conditioning, CAR-T cell dose, target selection and costimulatory molecule), the incidence rate (neutropenia, thrombocytopenia, anemia, AST increase, ALT increase, serum increase, APTT prolongation and fibrinogenopenia), and the onset and recovery time of hematological toxicity. And we two stored the information using Microsoft Excel for analysis. Disagreements were settled by discussion with the third reviewer.

Methodological quality of the included studies

We used a specific tool for evaluating the methodological quality of the non-comparative studies [7]. This tool is categorized into four domains: selection of patients, ascertainment of exposure and outcome, causality and reporting [7]. We assessed methodological quality of each study by grading the risk of bias as low (score of 0–1), moderate (score of 2–3) and high (score of 4).

Statistical analysis

We used the “Meta” and “Metafor” packages in the R-4.0.3 statistical software to analyze therapeutic safety. The incidence rates and relevant 95% confidence intervals (CIs) were calculated to estimate pooled results from studies. In case of no obvious heterogeneity ($I^2 < 50\%$ and $P \geq 0.05$ in the Q test), the results from fixed-effects model were reported in our meta-analysis. Otherwise, the results from random-effects model were reported. All pooled results with $P$-values $\leq 0.05$ were considered statistically significant. We performed the Egger’s test to assess statistically the publication bias ($P > 0.05$ was considered indicative of no significant publication bias), and funnel plots were constructed for providing a visual analysis of publication bias. Sensitivity analysis was conducted for estimating the effect on the overall rates of neutropenia, thrombocytopenia and anemia, with removal of the corresponding studies one by one. Subgroup analysis by age ($< 45$ vs. $\geq 45$ and $< 60$ vs. $\geq 60$), target antigen selected (CD19 vs. no CD19), co-stimulatory molecule (41BB vs. CD28), proportion of previous HSCT ($< 50\%$ vs. $\geq 50\%$), and the median lines of prior therapy ($< 4$ vs. $\geq 4$) was performed to explore the sources of heterogeneity, and $Z$ test was conducted for comparing the merged incidence rates between subgroups.

Results

Literature search and study characteristics

Two thousand ninety potentially relevant studies were retrieved, and 356 studies were de-duplicated by EndNote X9. By screening titles and abstracts, 666 reviews, 51 case reports, 80 basic studies and 712 studies with irrelevant topic were excluded. After full texts were carefully reviewed, among studies based on the same data sources, we only included one with the most recent updated results of clinical trials. Besides, 132 studies with insufficient data were excluded. One additional study was included by cross searching the references of previous meta-analysis. Finally, 52 eligible studies involving 2004 patients were included [8–59]. The flowchart describing the literature selection process is presented in Fig. 1. The characteristics of the included studies is shown in Table 1. Of the included studies, 47 (90%) explored the incidence rate of hematological toxicity, 20 (38%) explored the hepatic toxicity, 10 (19%) explored the renal toxicity and 11 (21%) explored the coagulation dysfunction related to CAR-T cell therapy. The detailed features of the included patients in their corresponding studies are presented in Table 2. As shown, the target patients of included studies were those with lymphoma, leukemia or MM. The proportion of male was 39–100%; the median patients age ranged from 7.5 to 67 years; the median lines of prior therapy ranged from 3 to 7; and the proportion of prior HSCT was 0–100%. Based on the assessment of quality, the included studies had a risk bias of low or moderate (Table 3).

Hematological toxicity

Overall incidence rate

Forty-six studies [8, 10–16, 18–25, 27, 28, 30–32, 34, 35, 37–52, 54–56, 58–61] reported the incidence rates of hematological toxicity. Of these, 40 studies [8, 10–12, 14–16, 18–28, 30, 32, 34, 35, 37–42, 44, 46–52, 55, 56, 58, 59] involving 1652 patients explored the rate of neutropenia, 41 [8–16, 18–28, 30–32, 34, 35, 37–46, 48, 49, 52, 54, 56, 59] studies involving 1619 patients explored the rate of thrombocytopenia, and 40 [8–11, 13, 14, 16, 18–25, 27, 28, 30–32, 35, 37, 39–47, 49–52, 54–56, 58, 59] studies involving 1638 patients explored the rate of anemia. As shown in Fig. 2, the total incidences of neutropenia, thrombocytopenia and anemia of any grades were 80% (95% CI: 68–89%), 61% (95% CI: 49–73%), and 68% (95%CI: 54–80%) respectively. And the pooled results of grade $\geq 3$ neutropenia, thrombocytopenia and anemia were 60% (95% CI: 49–70%), 33% (95% CI: 27–40%), and 32% (95%CI: 25–40%) respectively. The pooled results are shown in Table 4 in detail.
Subgroup analysis
We performed subgroup analysis for age, pathological type, target antigen, co-stimulatory molecule, the proportion of previous HSCT and median lines of prior therapy.

We set the age into three groups as low (< 45 years old), middle (≥ 45 and < 60 years old) and high (≥ 60 years old). The pooled results showed younger patients were more likely to experience hematological toxicity but with no statistical significance. According to pathological type, we analyzed the toxicity among patients with lymphoma, leukemia or MM and the result is presented in Tables 5 and 6. Subgroup analysis of target antigen (CD19 vs. no CD19) revealed that non-CD19 cases had the higher rate of hematological toxicity. Especially in analyzing neutropenia, Z test illustrated that the difference between the two groups (CD19 vs. no CD19) was of statistical significance. For neutropenia of any grades, the pooled result of any grades anemia was of statistical significance and the P-value of the Z test was 0.0424. Given that patients with leukemia were younger than lymphoma and MM overall from our extracted data, we set these patients into two group as < 20 and ≥ 20. The results revealed that the incidences of hematological toxicity were regularly higher in the older cases, and the P-value of Z test was 0.032 in any grades thrombocytopenia. For MM, because the studies were not adequate as lymphoma and leukemia, we only performed subgroup analysis by age (< 60 vs. ≥ 60 years old) for grade ≥ 3 hematological toxicity. The results showed that the hematological toxicity was more frequent in ≥ 60 cases, and the P-values of Z test were statistically significant in grade ≥ 3 neutropenia and thrombocytopenia (0.0227 and 0.0356, respectively). The detailed results are shown in Tables 5 and 6.

Aiming to specifically analyze the effect of co-stimulatory molecule on hematological toxicity, we eliminated the confounding factor targeting antigen and chose the part with the most sufficient data. The selected studies focused on lymphoma patients treated with CAR-T cell targeting CD19, and we explored the different effects of co-stimulatory molecule (CD28 vs. 41BB) with the
| Name                | Type of literature | Journal                      | Year Published | Trial sequence | Design | Sample | Pre-infusion conditioning | Dose                  | Target | Costimulatory domain | AEs criteria |
|---------------------|--------------------|------------------------------|----------------|----------------|--------|--------|---------------------------|-----------------------|--------|---------------------|--------------|
| Ying Zhita, a       | Journal            | Molecular Therapy- Oncolytics | 2019           | NCT03528421    | phase 1/2 | 3      | CF                         | 5*10^5/kg            | CD19   | CD28                | CTCAE v5.0   |
| Ying Zhita, a       | Journal            | Molecular Therapy- Oncolytics | 2019           | NCT03528421    | phase 1/2 | 3      | CF                         | 5*10^5/kg            | CD19   | 41BB                | Not found    |
| Yan, Zi-Xun         | Journal            | Clinical Cancer Research     | 2019           | NCT03355859    | phase 1  | 10     | CF                         | (2.5 or 5 or 10) *10^7 | CD19   | CD19                | CTCTAE v4.03 |
| Sang, W             | Journal            | Cancer Med                   | 2020           | NCT03207178    | phase 2  | 21     | CF/fosfamide               | CD19: 1.0 (0.2–4.0) *10^6/kg CD20: 0.9*(0.1–40) *10^6/kg | CD19 + CD22 | CD28 + 41BB        | CTCTAE v4.03 |
| Tong, C             | Journal            | Blood                        | 2020           | NCT03097770    | phase 1/2a | 28     | CF-based                  | 0.5*10^6–6*10^6/kg   | CD19 + CD20 | 41BB                | CTCAE v4.0   |
| Xu, J               | Journal            | PNAS                         | 2019           | NCT03090659    | phase 1  | 17     | CF/Cy-based               | 0.7(0.21–1.52) *10^6/kg | LCAR-B38M | 41BB                | CTCTAE v4.03 |
| Zhao, W. H          | Journal            | J Hematol Oncol              | 2018           | NCT03090659    | phase 1  | 57     | Cy                         | 0.5(0.07–2.1) *10^6/kg | LCAR-B38M | 41BB                | CTCTAE v4.03 |
| Shah, N. N          | Journal            | Nature Medicine              | 2020           | NCT03019055    | phase 1  | 22     | CF                         | (2.5 or 7.5 or 25)*10^5/kg | CD19 + CD20 | 41BB                | CTCAE v5.0   |
| Wang, Y             | Journal            | Int J Lab Hematol            | 2020           | NCT02782351    | phase 1/2 | 21     | CF                         | 1*10^6/kg            | CD19   | 41BB                | CTCTAE v4.03 |
| Fried, S.           | Journal            | Bone Marrow Transplant       | 2019           | NCT02772198    | phase1b/2 | 35     | CF                         |                          | CD19   | CD28                | Not found    |
| An, F               | Journal            | Nature Communications        | 2020           | NCT02735291    | phase 2  | 47     | CF/VDCP/Cy                 | (1–5)*10^6/kg ≤2*10^9 | CD19   | 41BB                | CTCTAE v4.03 |
| Ramos, C. A         | Journal            | Journal of Clinical Oncology  | 2020           | NCT02690545    | phase 1/2 | 42     | CF/Benda/ Benda-Flu        | 2*10^7cells/m2; 1*10^8cells/m2; 2*10^8 cells/m2 | CD30   | CD28                | CTCAE v4.0   |
| Raje, N             | Journal            | N Engl J Med                 | 2019           | NCT02658929    | phase 1  | 33     | CF                         | 50 、 150 、 450 、 800*10^6 | BCMA   | 41BB                | CTCTAE v4.03 |
| Abramson, J. S      | Journal            | Lancet                       | 2020           | NCT02631044    | phase 1  | 269    | CF                         | (50 or 10 or 150) *10^6 | CD19   | 41BB                | CTCTAE v4.03 |
| Wang, M             | Journal            | N Engl J Med                 | 2020           | NCT02601313    | phase 2  | 68     | CF                         | 2*10^6/kg            | CD19   | 41BB                | CTCTAE v4.03 |
| Cohen, A. D         | Journal            | J Clin Invest                | 2019           | NCT02546167    | phase 1  | 25     | Cy                         | (1–5)*10^8            | BCMA   | 41BB                | CTCAE v4.0   |
| Name                  | Type of literature | Journal          | Year Published | Trial sequence | Design | Sample Pre-infusion conditioning | Dose                                | Target | Costimulatory domain | AEs criteria |
|-----------------------|--------------------|-------------------|----------------|----------------|--------|----------------------------------|-------------------------------------|--------|----------------------|--------------|
| Goto, H               | Journal            | Int J Clin Oncol  | 2020           | NCT02445248    | phase 2| 9                               | CF or Benda 2*(1–4.9)*10^8         | CD19   | 41BB                 | CTCAE v4.03  |
| Schuster, S. J        | Journal            | N Engl J Med      | 2018           | NCT02445248    | phase 2a| 111                             | CF/Benda 3(0.1–6)*10^8 cells       | CD19   | 41BB                 | CTCAE v4.03  |
| Ghorashian, S         | Journal            | Nat Med           | 2019           | NCT02443831    | phase 1| 14                              | CF/Cy 10^6/kg or 0.73–0.78*10^6/kg | CD19   | 41BB                 | CTCAE v4.03  |
| Maude, S. L           | Journal            | N Engl J Med      | 2018           | NCT02435849    | phase 1/2a| 75                             | CF mainly 2.9(5SD12)*10^7/kg        | CD19   | 41BB                 | CTCAE v4.03  |
| Strati, Paolo         | Journal            | Haematologica     | 2020           | NCT02348216    |           | 31                              | CF 2*10^6/kg                        | CD19   | CD28                 | CTCTAE v4.03 |
| Locke, F. L           | Journal            | Lancet Oncol      | 2019           | NCT02348216    | phase 1/2| 108                             | CF 2*10^6/kg                        | CD19   | CD28                 | CTCTAE v4.03 |
| Fry, T. J             | Journal            | Nature medicine   | 2017           | NCT02315612    | phase 1| 21                              | (3 or 10 or 30)*10^5/kg            | CD22   | 41BB                 | Not found    |
| Ali, S. A             | Journal            | Blood             | 2016           | NCT02215967    | phase 1| 12                              | CF (0.3 or 1 or 3 or 9)*10^6/kg     | BCMA   | CD28                 | CTCAE v4.02  |
| Enblad, Gunilla       | Journal            | Clin Cancer Res   | 2018           | NCT02132624    | phase 1/2a| 15                             | CF (2–20)*10^6 cells/m2             | CD19   | CD28 + 41BB         | Not found    |
| Schuster, S. J        | Journal            | N Engl J Med      | 2017           | NCT02030834    | case-series| 28                             | Cy/EPOCH/Benda/Radio+Cy/etoposide+Cy/CBP+GEM 5.79(3.06–8.87)*10^6/Kg | CD19   | 41BB                 | Not found    |
| Gardner, R. A         | Journal            | Blood             | 2017           | NCT02028455    | phase 1/2| 43                             | CF/Cy (l or 5 or 10)*10^6/kg        | CD19   | 41BB                 | CTCAE v4     |
| Curran, K. J          | Journal            | Blood             | 2019           | NCT01860937    | phase 1| 25                              | CF/Cy (l or 3)*10^6/kg             | CD19   | CD28                 | CTCTAE v4.03 |
| Ramos, Carlos A       | Journal            | Molecular Therapy | 2018           | NCT01853631    | phase 1| 16                              | CF (l or 5 or 20)*10^6 cells/m2     | CD19   | CD28 + 41BB(2nd + 3st generation) | CTCTAE v4    |
| Zhang, W. Y           | Journal            | Signal Transd.    | 2016           | NCT01735604    | phase 2a| 11                              | Cy-based (0.41–1.46)*10^7/kg        | CD20   | 41BB                 | CTCAE v3.0   |
| Lee, D. W             | Journal            | Lancet            | 2014           | NCT01593696    | phase 1| 19                              | CF (l or 3)*10^6/kg                | CD19   | CD28                 | CTCAE v4.02  |
| Geyer, M. B           | Journal            | Mol Ther          | 2018           | NCT01416974    | phase 1| 8                               | Cy (3 or 10 or 30)*10^7             | CD19   | CD28                 | CTCAE v4     |
| Geyer, M. B           | Journal            | JO Insight        | 2019           | NCT00466531    | phase 1| 20                              | Cy or CF or Benda (0.4–3.0)*10^7/kg | CD19   | CD28                 | CTCAE v3.0   |
| Name                  | Type of literature | Journal                                      | Year Published | Trial sequence | Design            | Sample | Pre-infusion conditioning | Dose                              | Target         | Costimulatory domain | AEs criteria |
|-----------------------|--------------------|----------------------------------------------|----------------|----------------|-------------------|--------|---------------------------|-----------------------------------|----------------|----------------------|--------------|
| Sesques, P             | Journal            | American Journal of Hematology               | 2020           | commercial CAR T cells | retrospectively    | 33     | CF/Benda                 | Not found                       | CD19           | 41BB                 | CTCAE v5.0   |
| Sesques, P             | Journal            | American Journal of Hematology               | 2020           | commercial CAR T cells | retrospectively    | 28     | CF                        | Not found                       | CD19           | CD28                 | CTCAE v5.0   |
| Wang, N               | Journal            | Blood                                        | 2019           | ChCTR-OPN-16008526 | a pilot study      | 51     | CF                        | CD19:2.6±1.5*10^6/kg; CD22:2.7±1.2*10^6/kg | CD19+CD22     | CD28+41BB            | CTCTAE v4.03 |
| Wang, N               | Journal            | Blood                                        | 2019           | ChCTR-OPN-16008526 | a pilot study      | 38     | CF                        | CD19–5.1±2.1*10^6/kg; CAR22–5.3±2.4*10^6/kg | CD19+CD22     | CD28+41BB            | CTCTAE v4.03 |
| Zhou, X               | Journal            | Frontiers in Immunology                      | 2020           | ChCTR-OOC-16007779 | phase 1            | 21     | CF                        | 8.9(0.3–48)*10^5/kg              | CD19 forth generation |                   | CTCTAE v4.03 |
| Wang, Jia             | Journal            | British Journal of Haematology               | 2020           | ChCTR-ONN-16009862+ChCTR1800019622 | a pilot study      | 23     | CF                        | 1*10^6/Kg                       | CD19           | 41BB                 | CTCAE v4.0   |
| Zhiling Yan           | Journal            | Lancet Haematol                             | 2019           | ChCTR-ROIC-17,011,272 | phase 2            | 21     | CF                        | 1*10^6/kg                       | CD19+BCMA      | 41BB                 | CTCAE v4.0   |
| Bao, F                | Journal            | Zhonghua xueyexue zazhi                     | 2018           | case-series     |                   | 10     | CF                        | 4.27(0.30–6.93)*10^6/kg           | CD19           | 41BB                 | CTCAE v4.0   |
| Jain, T               | Journal            | Blood Advances                              | 2020           | NCT01044069; NCT03070327; commercial CART cells | clinical trials; retrospectively | 83     | CF/Gy/Bendam              | Not found                       | CD19+BCMA      | CD28+41BB            | CTCAE v5.0   |
| Popat, R              | Abstract           | Blood                                        | 2019           | NCT03287804     | phase 1            | 11     | CF                        | (15 or 75 or 225 or 600 or 900)*10^6 | BCMA+TACI     | CD28+OK40            | Not found    |
| Usmani, S. Z          | Abstract           | HemaSphere                                   | 2020           | NCT03548207     | phase 1b           | 29     | CF                        | 0.73(0.5–0.9)*10^6/kg           | BCMA           | 41BB                 | CTCAE v5.0   |
| Mailankody, S         | Abstract           | HemaSphere                                   | 2020           | NCT034330011    | phase 1/2          | 51     | CF                        | (300 or 450 or 600)*10^6         | BCMA           | 41BB                 | Not found    |
| Hu, Jianda            | Abstract           | Blood                                        | 2018           | NCT03391726     | phase 2/3          | 8      | CF                        | (0.7–6)*10^6/kg                 | CD19           | 41BB                 | Not found    |
| Name                | Type of literature | Journal                      | Year Published | Trial sequence                  | Design               | Sample | Pre-infusion conditioning | Dose                          | Target                  | Costimulatory domain | AEs criteria |
|---------------------|--------------------|-------------------------------|----------------|-------------------------------|----------------------|--------|---------------------------|-------------------------------|------------------------|----------------------|--------------|
| Amrolia, Persis J.  | Abstract           | Blood                         | 2018           | NCT03287817                   | phase 1; AUTO3       | 8      |                          | (1 or 3 or 5)*10^6/kg       | CD19 + CD22             | OX40(CD19); 41BB(CD22) | Not found   |
| Ardesna, Kirit      | Abstract           | Blood                         | 2019           | NCT03287817                   | phase 1/2; AUTO3     | 11     |                          | (50 or 150)*10^6           | CD19 + CD22             | OX40(CD19); 41BB(CD22) | Not found   |
| Yan, Lingzhi        | Abstract           | Blood                         | 2019           | NCT03196414                   | phase 1/2            | 28     |                          | CD19*10^6/kg; BCMA(2–6.8) x 10^7/kg | CD19 + BCMA             | 41BB       | Not found   |
| Wierda, William G   | Abstract           | Blood                         | 2018           | NCT02614066                   | phase 1              | 35     |                          | (0.5 or 1 or 2)*10^6/kg     | CD19                   | 41BB       | Not found   |
| Topp, M. S.         | Abstract           | Hematological Oncology        | 2019           | NCT02348216                   | ZUMA-1 updated      | 21     |                          | 2*10^6/kg                    | CD19                   | CD28       | Not found   |
| Jiang, Songfu       | Abstract           | Blood                         | 2018           |                               | sponsored-clinical trial | 16     |                          | (0.5 or 1.8 or 1.5)*10^8     | BCMA                   | 41BB       | Not found   |
| Dourthe, M. E       | Abstract           | Blood                         | 2019           |                               | sponsored-clinical trial | 41     |                          | (2–5)*10^6/kg; (weight ≤ 50 kg); (1–2.5)*10^8/kg (weight > 50 kg) | CD19                   | 41BB       | Not found   |
| Jacobson, Caron      | Abstract           | Blood                         | 2020           | NCT03105336                   | phase 2              | 146    |                          | 2*10^6/kg                    | CD19                   | CD28       | CTCAE v4.03 |
| WayneAS             | Abstract           | Hemasphere                    | 2019           | NCT02625480                   | phase 1              | 24     |                          | 1 or 2*10^6/kg              | CD19                   | 41BB       | Not found   |

1. The two are from the same article. The co-stimulatory molecule of the former dataset is CD28, and that of the latter dataset is 41BB.
2. 21 patients were included in this article, but 19 patients were analyzed for evaluating hematological toxicity.
3. The two are from the same article. Axicabtagene ciloleucel is used in the former dataset and tisagenlecleucel is used in the latter dataset.
4. The two are from the same article. The former data was focusing on the patients with ALL (acute lymphocytic leukemia) and the latter data was focusing on the patients with NHL (Non-Hodgkin Lymphoma).
Table 2  Basic characteristics of the included patients

| Name                     | Disease               | Sample | Sex (male%) | Age [median(range)] | Prior therapy lines | HSCT% |
|--------------------------|-----------------------|--------|-------------|---------------------|---------------------|-------|
| Abramson, J. S           | lymphoma              | 269    | 65%         | 63(54–70)           | ≥3 lines: 51%       | 35%   |
| Zhiling Yan              | MM                    | 21     | 48%         | 58(49.5–61)         | mean lines: 6       | 14%   |
| Ali, S. A                | MM                    | 12     |             |                     | median lines: 7     | 100%  |
| Cohen, A. D              | MM                    | 25     | 68%         | 58(44–75)           | median(range) lines: 7(3–13) | 92%   |
| Curran, K. J             | ALL                   | 25     |             | 13.5(1–22.5)        | Not found           | 20%   |
| Enblad, Gunilla          | lymphoma+ALL          | 15     | 47%         | 61(24–71)           | mean lines: 1.73    | 40%   |
| Fry, T. J                | B-ALL                 | 21     | 62%         | 19(7–30)            | Not found           | 90%   |
| Gardner, R. A            | B-ALL                 | 43     | 44%         | 12.3(1.3–25.4)      | Not found           | 62%   |
| Geyer, M. B              | CLL                   | 8      | 100%        | 58(45–70)           | median(range) lines: 4(1–11) | 0     |
| Geyer, M. B              | CLL+NHLC              | 20     | 70%         | 63(43–75)           |                     |       |
| Goto, H                  | DLBCL                 | 9      | 56%         | 61(32–73)           | mean lines: 3       | 44.40%|
| Fried, S.                | ALL+NHLC              | 35     | 71%         | 27(3.5–55)          | Not found           | 37%   |
| Lee, D. W                | ALL+DLBCL             | 19     | 67%         | 1 to 30             | mean lines: 2       | 38%   |
| Locke, F. L              | lymphoma              | 108    | 68%         |                     | median(range) lines: 3 | 23%   |
| Maude, S. L              | ALL                   | 75     | 57%         | 11(3–23)            | median(range) lines: 3(1–8) | 61%   |
| Xu, J                    | MM                    | 17     | 65%         | 55(40–73)           | median(range) lines: 5(3–11) | 47%   |
| Schuster, S. J           | DLBCL                 | 111    | 65%         | 56 (22–76)          | ≥3 lines: 52%       | 49%   |
| Raje, N                  | MM                    | 33     | 64%         | 60(37–75)           | median(range) lines: 7(3–23) | 97%   |
| Schuster, S. J           | FCL+DLBCL             | 28     | 64%         | 57.5(25–77)         | median(range) lines: 4.5 (1–10) | 39%   |
| Wang, N                  | ALL                   | 51     | 63%         | 27 (9–62)           | Not found           | 24%   |
| Wang, N                  | NHL                   | 38     | 58%         | 47 (17–71)          | Not found           | 15.80%|
| Zhao, W. H               | MM                    | 57     | 60%         | 54 (27–72)          | median(range) lines: 3 (1–9) | 18%   |
| Wang, M                  | MM                    | 68     | 84%         | 65 (38–79)          | ≥3lines 81%; median(range) lines: 3 (1–5) | 43%   |
| Sang, W                  | DLBCL                 | 21     | 62%         | 55 (23–72)          | median(range) lines: 3 (1–6) | 5%    |
| Wayne AS,                | ALL                   | 24     | 63%         | 13(3–20)            | ≥3 lines: 42%       | 25%   |
| Ghorashian, S            | ALL                   | 14     | 93%         | 9.24 (1.35–19.28)   | median(range) lines: 4(2–7) | 71%   |
| Wang, J                  | ALL                   | 23     | 61%         | 42(10–67)           | median(range) lines: 2(2–3) | 22%   |
| Bao, F.                  | ALL+NHLC              | 10     | 40%         | 33.5(25–69)         | Not found           |       |
| Hu, Jianda               | DLBCL                 | 8      |             | 52(27–70)           | Not found           |       |
| Jiang, Songfu            | MM                    | 16     |             | 55 (39–67)          | median(range) lines: 4(2–10) | 56%   |
| Wierda,William G         | ALL                   | 35     | 51%         | 40(18–69)           | ≥3 lines: 60%       |       |
| Yan, Lingzhi             | MM                    | 28     | 82%         | 57.5 (42–69)        | mean(range) lines: 3(2–8) |       |
| Amrolia, Persis J        | ALL                   | 8      |             | 7.5(4–16)           | Not found           | 63%   |
| Ardeshina, Kirt          | DLBCL                 | 11     |             | 49                  | median lines: 3     | 27%   |
| Strati, Paolo            | lymphoma              | 31     | 74%         | 52(23–76)           | ≥3lines 45%; median(range) lines: 3 (1–11) | 35%   |
| Yan, Zi-Xun              | NHL                   | 10     | 80%         | 47(32–59)           | ≥3 lines: 100%      |       |
| Ying, Zhitao             | NHL                   | 3      | 67%         | <65                | mean lines: 9.7     | 0     |
| Ying, Zhitao             | NHL                   | 3      | 100%        | <65                | mean lines: 8       | 0     |
| Topp, M. S               | lymphoma              | 21     | 67%         | 63 (36–73)          | ≥2lines: 76%        | 10%   |
| An, F                    | ALL                   | 47     | 49%         | 22(3–72)           | <10lines: 59.6%     | 19.10%|
| Dourthe, M. E            | ALL                   | 41     |             | 18.2(1–29.2)        | Not found           | 63%   |
| Mailankody, S            | MM                    | 51     |             | 61(33–77)          | median(range) lines: 6 (3–18) |       |
| Popat, R                 | MM                    | 11     |             | 61 (45–69)          | median(range) lines: 5(3–6) | 73%   |
extracted data. As shown in Tables 5 and 6, the results showed that the hematological toxicity was more frequent in cases where the co-stimulatory molecule was CD28, and the Z tests showed that the differences were significant in analyzing thrombocytopenia and any grades anemia. In other words, the co-stimulatory molecule of CD28 has greater tendency to induce hematological toxic effects than that of 41BB. The conclusion is in line with previous studies reporting that 41BB CAR-T cells resulted in less severe AEs [62].

Onset time of hematological toxicity
In this part, we only conducted analysis qualitatively. The study by Fried S et al. [16] reported that the median time to onset of neutropenia was 3 days (range 0–21) and severe neutropenia occurred within a median of 7 days (range 0–63), and they reported that the median time to onset of thrombocytopenia was 0 days (range 0–38) and that of grade ≥ 3 was 5.5 days (range 0–28). That is, hematological occurred early in the process of CAR-T therapy. Besides, Wang J et al. [43] reported that grade ≥ 3 hematological toxicity mostly occurred 5 days after pretreatment. And in general, conditioning chemotherapy was conducted 3–5 days before infusion. It was reported that hematological toxicity after CAR-T was in fact associated with lymphodepleting chemotherapy [25]. However, even though it is pretreatment but not the CAR-T cell itself leading to hematological toxicity in mechanism, since conditioning regimen was an important part of CAR-T therapy procedure, we should conclude that CAR-T therapy was related to the toxicity of blood system. Furthermore, the facts listed above were important reminders for us to note the hematological toxic effects shortly after initiating CAR-T therapy.

Recovery time of hematological toxicity
We analyzed hematological toxicity on day 28 and on the 3rd month after infusion. However, because of the limitations of the extracted data, we only explored the grade ≥ 3 cytopenia, neutropenia and thrombocytopenia, and the calculated data is presented in Table 4. On D28 after infusion, the pooled results of grade ≥ 3 cytopenia, neutropenia and thrombocytopenia were 39% (95%CI: 24–55%), 13% (95%CI: 5–25%) and 25% (95%CI: 19–36%) respectively. On the 3rd month, the grade ≥ 3 neutropenia was 5% (95%CI: 0–16%), and grade ≥ 3 thrombocytopenia was 20% (95%CI: 8–35%). Both time points of day 28 and the 3rd month witnessed higher thrombocytopenia than neutropenia. And as shown in Table 4, the overall incidences of neutropenia were more frequent than thrombocytopenia. An explanation is that platelets are more difficult to recover than neutrophils, consistent with the conclusion of one study by Jain T et al. [46]. They demonstrated that hematological count “normalization” (in the normal range for the laboratory) was much easier for neutrophils than hemoglobin and platelets.

Sensitivity analysis and publication bias
Sensitivity analysis was performed in overall rate of the hematological toxicity. And the results showed that after omitting the studies one by one, the pooled results did not change significantly. In other words, the results of the meta-analysis were stable enough (Fig. 3). Egger test was
conducted for analyzing publication bias in evaluating overall incidences of neutropenia, thrombocytopenia and anemia. If *P* value > 0.05 was met in analyzing, it was considered as having no publication bias (data not shown). The funnel plots of Egger tests are shown in Fig. 4. Publication bias did not occur in all six groups.

Table 3  Risk of bias

| Study          | Selection | Ascertainment | Causality | Reporting | Risk of bias |
|----------------|-----------|---------------|-----------|-----------|--------------|
| Ying et al     |           | X             |           |           | Low          |
| Yan et al      |           | X             |           |           | Low          |
| Sang et al     |           | X             |           |           | Low          |
| Tong et al     |           | X             |           |           | Low          |
| Xu et al       |           | X             |           |           | Low          |
| Zhao et al     |           | X             |           |           | Low          |
| Shah et al     |           | X             |           |           | Low          |
| Wang et al     |           | X             |           | X         | Moderate     |
| Fried et al    |           | X             |           |           | Low          |
| An et al       |           | X             |           |           | Moderate     |
| Ramos et al    |           | X             |           |           | Moderate     |
| Raje et al     |           | X             |           |           | Low          |
| Abramson et al |           | X             |           |           | Moderate     |
| Wang et al     |           | X             |           |           | Moderate     |
| Cohen et al    |           | X             |           |           | Moderate     |
| Goto et al     |           | X             |           |           | Low          |
| Schuster et al |           | X             |           |           | Moderate     |
| Ghorashian et al |       | X             |           |           | Moderate     |
| Maude et al    |           | X             |           |           | Low          |
| Strati et al   |           | X             |           |           | Low          |
| Locke et al    |           | X             |           |           | Low          |
| Fry et al      |           | X             |           |           | Low          |
| Ali et al      |           | X             |           |           | Low          |
| Enblad et al   |           | X             |           |           | Low          |
| Schuster et al |           | X             |           | X         | Moderate     |
| Gardner et al  |           | X             |           |           | Low          |
| Curran et al   |           | X             |           |           | Low          |
| Ramos et al    |           | X             |           |           | Low          |
| Zhang et al    |           | X             |           |           | Low          |
| Lee et al      |           | X             |           | X         | Moderate     |
| Geyer et al    |           | X             |           |           | Low          |
| Geyer et al    |           | X             |           |           | Low          |
| Sesques et al  |           | X             |           |           | Low          |
| Wang et al     |           | X             |           |           | Low          |
| Zhou et al     |           | X             |           |           | Low          |
| Wang et al     |           | X             |           |           | Moderate     |
| Yan et al      |           | X             |           |           | Moderate     |
| Bao et al      |           | X             |           | X         | Moderate     |
| Jain et al     |           | X             |           |           | Low          |

Evaluation of methodological quality. Negative points are denoted with “X”. Score of 0–1 suggests low risk of bias, 2–3 moderate, and 4 high.

Coagulation toxicity

Pooling data of the data indicated that the incidences of any grades APTT prolongation and fibrinogenopenia were 56% (95%CI: 31–79%) and 13% (95%CI: 6–22%) respectively, and that proportion of ≥3 grade APTT prolongation and fibrinogenopenia were 4% (95%CI: 2–79%) and 5% (95%CI: 2–9%) (Table 4). Furthermore, we performed the subgroup analysis of any grades APTT
prolongation and fibrinogenopenia by pathological type (just in cases of “leukemia” and “MM”). As shown in Tables 5 and 6, the difference between the two subgroups was not statistically significant. The incidences of APTT prolongation were 50% (95% CI: 3–97%) and 39% (95% CI: 10–73%) in leukemia cases and MM cases respectively. And the pooled results showed that the rates of any grades fibrinogenopenia were comparable in the two subgroups of leukemia (12%) and MM (16%).

**Hepatotoxicity**

Meta-analysis showed that rates of any grades AST and ALT increasement were 28% (95% CI: 18–43%) and 29% (95% CI: 24–35%) respectively, and that incidences of grade ≥ 3 AST and ALT increasement were 6% (95% CI: 3–10%) and 2% (95% CI: 1–3%) (Table 4). We also performed subgroup analysis by pathological type in this part and the additional data is presented in Tables 5 and 6 in detail.

**Nephrotoxicity**

To explore the effect of CAR-T cell therapy on renal function, we conducted an analysis on data about...
### Table 5: Subgroup analysis of hematological toxicity

#### Any grades of hematological toxicity

| Median age (years) | Neutropenia | Thrombocytopenia | Anemia |
|-------------------|-------------|------------------|--------|
| < 45              | 82% (42–100%) | 74% (44–95%) | 79% (4–100%) |
| ≥45 and < 60      | 82% (64–96%) | 57% (39–75%) | 77% (59–92%) |
| > 60              | 72% (56–85%) | 50% (28–71%) | 53% (39–68%) |

| Pathological type | Neutropenia | Thrombocytopenia | Anemia |
|-------------------|-------------|------------------|--------|
| leukemia          | 62% (17–98%) | 60% (22–93%) | 69% (17–100%) |
| lymphoma          | 83% (73–90%) | 60% (46–73%) | 68% (54–80%) |
| MM                | 88% (64–100%) | 57% (36–77%) | 53% (21–84%) |

| Targeting antigen | Neutropenia | Thrombocytopenia | Anemia |
|-------------------|-------------|------------------|--------|
| CD19              | 73% (58–86%) | 56% (40–71%) | 64% (48–79%) |
| non-CD19          | 93% (84–99%) | 70% (54–83%) | 74% (46–95%) |

| Proportion of previous HSCT | Neutropenia | Thrombocytopenia | Anemia |
|-----------------------------|-------------|------------------|--------|
| < 50%                       | 80% (56–97%) | 74% (58–87%) | 74% (58–87%) |
| ≥50%                        | 77% (62–89%) | 52% (34–69%) | 49% (23–74%) |

| Median lines of prior therapy | Neutropenia | Thrombocytopenia | Anemia |
|-------------------------------|-------------|------------------|--------|
| < 4                            | 79% (61–93%) | 42% (27–58%) | 55% (43–67%) |
| ≥4                            | 81% (69–92%) | 67% (53–80%) | 65% (43–84%) |

| Co-stimulatory molecule | Neutropenia | Thrombocytopenia | Anemia |
|-------------------------|-------------|------------------|--------|
| CD28                    | 88% (82–93%) | 79% (59–94%) | 79% (64–92%) |
| 41BB                     | 65% (41–86%) | 36% (17–57%) | 55% (42–67%) |

| Median age in leukemia cases | Neutropenia | Thrombocytopenia | Anemia |
|------------------------------|-------------|------------------|--------|
| < 20                         | 61% (10–100%) | 45% (14–79%) | 45% (14–79%) |
| ≥20                          | 83% (38–100%) | 87% (66–99%) | 87% (66–99%) |

| Median age in lymphoma cases | Neutropenia | Thrombocytopenia | Anemia |
|------------------------------|-------------|------------------|--------|
| < 60                         | 85% (63–99%) | 59% (35–81%) | 80% (64–93%) |
| ≥60                          | 67% (51–81%) | 47% (23–72%) | 52% (34–69%) |

#### ≥3 grade of hematological toxicity

| Median age (years) | Neutropenia | Thrombocytopenia | Anemia |
|-------------------|-------------|------------------|--------|
| < 45              | 57% (28–84%) | 33% (20–47%) | 38% (22–56%) |
| ≥45 and < 60      | 59% (40–76%) | 32% (22–43%) | 34% (22–46%) |
| > 60              | 59% (45–71%) | 32% (23–43%) | 28% (18–40%) |
serum creatine elevated (SCE). As shown in Table 4, the proportion of any grades SCE was 14% (95%CI: 8–24%), and the incidences of grade ≥ 3 SCE were quite low. Given that the extracted data of nephrotoxicity was not rich, we did not perform subgroup analysis in this section.

**Discussion**

CAR-T cell therapy has dramatical efficacy in hematological malignancies and is developing continuously. There are many articles exploring the pooled complete remission, and the incidence of CRS, as the characteristic adverse effect of CAR-T therapy. However, no study specifically reported the relevant hematological toxicity, coagulation toxicity, hepatotoxicity and nephrotoxicity. The purpose of our meta-analysis was to fill this gap and the main aim was evaluating hematological toxicity after CAR-T infusion.

This meta-analysis showed that the incidence rate of grade 3/4 neutropenia, thrombocytopenia and anemia were 60, 33 and 32%, respectively during CAR-T treatment. For lymphoma, these incidences were 60, 32 and 24% correspondingly. For leukemia, they were 48, 28 and 41% correspondingly. For MM, they were 58, 40 and 31%
correspondingly. Compared with grade 3/4 CRS from previous reviews [63–65], our pooled results indicated that the most common grade $\geq 3$ AEs were hematological toxic effects. Based on I² statistic, the results from random-effect model were used to represent overall hematological toxicity. At the same time, subgroup analysis did not reduce heterogeneity. According to subgroup analysis and the corresponding Z test, hematological toxicity is more frequent in younger patients, in patients with $\geq 4$ median lines of prior therapy and in cases targeting CD19. With specific regards to anti-CD19 CAR-T cell constructs, we focused on lymphoma to explore the difference of hematological toxicity between CD28 and 41BB, as two main co-stimulatory molecules in CAR-T therapy. Consistent with our expectations and similar with other AEs, hematological toxicity was more likely to occur in CD28 cases [62]. Some studies reported that patients with severe neutropenia died from severe infections, and some patients with severe thrombocytopenia died because of intracranial hemorrhage or other life-threatening bleeding events [11, 21, 28, 43, 44, 66]. In long-term follow-up after CAR-T therapy, most delayed hematological toxicities were not life-threatening and would ameliorate 3 months after treatment [28, 46]. This reminds us of paying attention to hematological toxicities in the early process of CAR-T therapy. Hepatotoxicity, nephrotoxicity and coagulation disorder are less frequent, compared with hematological toxicity, CRS and ICANS. All of these AEs can reflect the levels of inflammation in patients treated with CAR-T cell, and this meta-analysis provided the pooled results to clinicians for reference.

Cytokine release is a double-edged sword as high cytokine levels can result in severe AEs [70]. CRS, the

| Pathological type | Subgroup analysis of non-hematological toxicity |
|------------------|-----------------------------------------------|
|                  | Any grades of Coagulation toxicity             |
|                  |                                        | APTT prolonged | Fibrinogen decreased |
| leukemia         | rate                                        | 50% (3–97%)    | 12% (7–41%)          |
|                  | N                                           | 98             | 118                  |
| MM               | rate                                        | 59% (19–94%)   | 16% (1–41%)          |
|                  | N                                           | 123            | 103                  |
|                  | Any grades of Hepatic toxicity               |
|                  |                                        | AST increased  | ALT increased        |
| leukemia         | rate                                        | 25% (18–32%)   | 34% (24–44%)         |
|                  | N                                           | 154            | 93                   |
| lymphoma         | rate                                        | 24% (16–34%)   | 21% (15–27%)         |
|                  | N                                           | 249            | 249                  |
| MM               | rate                                        | 44% (14–77%)   | 25% (19–32%)         |
|                  | N                                           | 120            | 188                  |
|                  | $\geq 3$ grade of Hepatic toxicity           |
|                  |                                        | AST increased  | ALT increased        |
| leukemia         | rate                                        | 7% (3–12%)     | 4% (1–7%)            |
|                  | N                                           | 236            | 250                  |
| lymphoma         | rate                                        | 1% (0–4%)      | 1% (0–3%)            |
|                  | N                                           | 249            | 249                  |
| MM               | rate                                        | 16% (9–25%)    | 1% (0–4%)            |
|                  | N                                           | 132            | 200                  |

Cytokine release is a double-edged sword as high cytokine levels can result in severe AEs [70]. CRS, the
most common toxicity of CAR-T cell therapy, is triggered by engagement of their CARs with the antigen expressed on tumor cells [3]. Hematological toxicities potentially leading to additional complications such as infection or hemorrhage are also associated with cytokine release after CAR-T cell infusion. The study published recently proposed that improved CRS management may improve hematopoietic recovery following CD19 CAR T-cell therapy [4]. Management for CRS and ICANS has been specialized and the related guideline is being constantly being optimized. As hematological toxicities often occur after lymphodepleting chemotherapy, antiviral prophylaxis, i.e. acyclovir, should be started with pretreatment. Antimicrobial and antifungal prophylaxis may be considered when severe or persistent neutropenia happened [71]. Additionally, extended growth factors and transfusional support are needed for hematopoietic recovery [4, 72]. Meanwhile, symptomatic treatment, such as antibiotics and rehydration therapy, and professional nursing are important as well.
CAR-T cell therapy has achieved dramatical efficacy in ALL, B cell lymphoma and MM, but not in acute myeloid leukemia (AML). What limited the use of CAR-T cell in AML is the absence of specific antigen, as many myeloid antigens also expressed on hematopoietic stem cells which would lead to myelosuppression [3, 73]. Therapeutic approach still needs to be optimize to improve the efficacy and safety of CAR-T cell therapy, such as questing more specific antigens, improving CAR structure, professional management during the CAR-T therapy and application of combination of CAR-T cell and other therapies [71, 72, 74]. Recently, the clinical study showed that CD19-directed CAR-T cell with concurrent ibrutinib for relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) led to high rates of MRD-negative with low CRS severity [75].

Compared with previous meta-analysis about CAR-T treatment, the study holds some advantages. We included more studies and targeted not only a single pathological type. Besides, we aimed to analyze hematological toxicity during CAR-T therapy, which was not reported by other systematical reviews. Thirdly, we performed subgroup analysis by age, pathological type, targeting antigen, co-stimulatory molecule, proportion of HSCT and median lines of prior lines. In addition, we also analyzed hepatotoxicity, nephrotoxicity and coagulation disorder, all of which should be paid attention to but have not been explored previously.
This meta-analysis has some limitations as well. Firstly, we defined all kinds of lymphoma (DLBCL, MCL, HL, etc.) as "lymphoma", and we set all kinds of leukemia into the "leukemia" subgroup. Some studies pooled all patients with different pathological types together and analyzed the efficacy and safety of CAR-T therapy. When extracting the data in this situation, we deemed the subgroup as the pathological type in majority of the patients included in the study. For example, the study by Shah N. N. et al. [14] included 11 DLBCL patients, 7 MCL patients, 1 FCL patient and 3 CLL patients, so we categorized them as "lymphoma". This method of classification biased the pooled results. Secondly, some studies provided mean lines but not median lines of prior therapy. According to the statistics principle that both mean and median stand for the central tendency of the relevant data, we deemed the mean lines as the corresponding median lines roughly. Additionally, we included some conference proceedings to extract data for analyzing. The data was not detailed as those published in journals, and it might bring bias.

Conclusions
In conclusion, the CAR-T therapy is associated with hematological toxic effects. And some cases died from infections or severe hemorrhage in early period. In long-term follow-up, the majority of hematological toxicity is less life-threatening and most patients will ameliorate after 3 months. However, more work is needed to explore its mechanism. The significance of this study is to provide the pooled results to clinicians for reference, and to remind them of paying attention to prevention and intervention for hematological toxicity in the early process of CAR-T therapy.

Abbreviations
CAR: Chimeric antigen receptor-modified; HSCT: Hematopoietic stem cell transplantation; AST: Aspartate transaminase; ALT: Alanine transaminase; APTT: Activated partial thromboplastin time; CI: Confidence interval; mM: Multiple myeloma; scFv: Single-chain variable fragment; ICANS: Immune effector cell-associated neurotoxicity syndrome AE: adverse effect, CRS: Cytokine release syndrome; SCE: Serum creatine elevated; MDS: Myelodysplastic syndrome; DLBCL: Diffuse large B cell lymphoma; MCL: Mantle cell lymphoma; HL: Hodgkin lymphoma; FCL: Follicular cell lymphoma; CLL: Chronic lymphocytic leukemia; R/R: Relapsed/refractory.

Supplementary Information
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Additional file 1. PRISMA. Checklist.

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Authors’ contributions
Conception and design of study: HY, MH, LWJ. Acquisition of data: LWJ, LCG, KHM. Analysis and/or interpretation of data: LWJ, ZYQ, DMY. Drafting and revision of manuscript: LWJ, LC. All authors have read and approved the manuscript.

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Availability of data and materials
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Competing interests
The authors declare that they have no competing interests.

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