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Hematologic and lymphatic disorders associated with chimeric antigen receptor T-cell therapy: a pharmacovigilance analysis of the FDA adverse event reporting system (FAERS) database

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Abstract

Background As the application of Chimeric Antigen Receptor T-cell (CAR-T) therapy in cancer treatment becomes increasingly widespread, associated hematologic and lymphatic system adverse events pose significant challenges to its clinical use. Therefore, we aim to comprehensively investigate and summarize the hematologic and lymphatic system AEs associated with CAR-T therapy.

Methods We extracted CAR-T-related adverse event reports from the FDA Adverse Event Reporting System (FAERS) database for the period from August 2017 to December 2023. Disproportionality analysis using the Reporting Odds Ratio (ROR) and Information Component (IC) was performed to identify CAR-T-associated hematologic and lymphatic system AEs. We employed LASSO regression analysis to identify hematologic and lymphatic system AEs associated with mortality.

Results In the FAERS database, we identified 1,600 individual case safety reports of hematologic and lymphatic system AEs related to CAR-T therapy. The median age of patients was 57 years (interquartile range [IQR] 32–67), with fatal outcomes in 15.3% of cases. We identified 25 significant adverse event signals associated with CAR-T therapy. B-cell aplasia (ROR025 = 1054.56, IC025 = 4.74), cytopenia (ROR025 = 17.27, IC025 = 3.81), hypofibrinogenemia (ROR025 = 100.18, IC025 = 2.46), anemia (ROR025 = 1.87, IC025 = 0.59), febrile bone marrow aplasia (ROR025 = 55.32, IC025 = 2.70), and pancytopenia (ROR025 = 7.18, IC025 = 1.42) were the most significant hematologic and lymphatic system AEs for tisa-cel, axi-cel, brexu-cel, liso-cel, ide-cel, and cilta-cel, respectively. Most hematologic and lymphatic system AEs occurred within 10 days post-CAR-T infusion. Hematologic and lymphatic system AEs were associated with a mortality rate of 15.3%. Our analysis revealed 15 hematologic and lymphatic system AEs closely associated

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with mortality in CAR-T-treated patients, including splenic hemorrhage, disseminated intravascular coagulation, and pancytopenia.

Conclusions Our study found that hematologic and lymphatic system AEs were more closely associated with anti-CD19 CAR-T and CAR-T containing CD28. Splenic hemorrhage, disseminated intravascular coagulation, and pancytopenia were identified as hematologic and lymphatic system AEs that, while less frequently reported clinically, were highly associated with mortality.

Keywords CAR-T therapy, Hematologic and lymphatic system toxicity, Adverse events, FAERS

Introduction

Chimeric antigen receptor T-cell (CAR-T) therapy has become a crucial component in cancer treatment, achieving unprecedented success in hematological malignancies. It has significantly improved the prognosis for patients with relapsed/refractory hematological malignancies, including B-cell acute lymphoblastic leukemia (B-ALL), large B-cell lymphoma (LBCL), mantle cell lymphoma (MCL), and multiple myeloma (MM). Currently, CD19 and BCMA are the most common targets in CAR-T cell therapy. CD19 is expressed on various differentiated B-lineage cells and malignant B cells, while BCMA is a plasma cell-selective protein highly expressed on MM cells, mature B cells, and normal plasma cells [1, 2]. Consequently, CD19- and BCMA-targeted cells have demonstrated excellent antitumor activity in B-cell malignancies [2, 3].

In 2017, the U.S. Food and Drug Administration (FDA) approved the first CAR-T cell therapy, tisagenlecleucel (tisa-cel), for B-ALL and LBCL [1]. As of June 2024, six CAR-T cell therapies have been approved, including three additional CD19-specific CAR-T cell therapies: axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) for LBCL, and brexucabtagene autoleucel (brexu-cel) for MCL [4–6]. Two BCMA-specific CAR-T cell therapies have been approved for MM: idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) [7, 8].

Although CAR-T therapy has made significant breakthroughs in cancer treatment, associated adverse events remain a major challenge. The high toxicity and mortality risk of CAR-T cell therapy have hindered its adoption as a first-line treatment [9]. Severe toxicities associated with CAR-T cell therapy can impact its efficacy, with the most commonly reported adverse events being cytokine release syndrome (CRS), neurotoxicity, and hematological toxicity [10]. These related adverse events can be severe and even life-threatening if not managed with prompt and effective interventions [11]. CAR-T products differ in target antigen expression (e.g., CD19 on B cells vs. BCMA on plasma cells), and co-stimulatory domains (CD28 vs. 4-1BB), all of which may influence toxicity profiles. The design of different CAR-T products is different (Supplementary Table S5).

Hematologic and lymphatic system adverse events (AEs) are among the categories of CAR-T-related adverse reactions and are the most common long-term adverse events following CAR-T treatment, often accompanied by serious consequences [12]. The incidence rates and severity of symptoms vary among different adverse events. CAR-T-related hematologic and lymphatic system toxicities have been reported in several clinical trials and post-marketing studies. Clinical trials of CD19-targeted CAR-T therapies have shown frequent occurrence of ≥ grade 3 cytopenias following CAR-T cell treatment. In the ZUMA-1 and JULIET trials, 31% and 17% of treated patients experienced ≥ grade 3 febrile neutropenia, respectively, with severe cytopenias observed for more than 30 days post-administration [1, 4, 13–15]. Neutropenia, thrombocytopenia, and anemia are common after CAR-T cell infusion (94%, 80%, and 51%, respectively) [10]. Shi X's clinical trial study on BCMA-targeted CAR-T therapy also demonstrated that grade 3 or higher hematologic toxicities were the most common adverse events, including lymphopenia (100%), neutropenia (20%), anemia (50%), and thrombocytopenia (70%) [16]. However, CAR-T clinical trial data, with strict inclusion criteria and limited participant numbers, may not fully reflect real-world situations and could lead to underestimation of hematologic and lymphatic system AEs.

Given the complexity, severity, and various influencing factors of CAR-T-related hematologic and lymphatic system AEs, the number of pharmacovigilance post-marketing studies reporting on these issues is increasing [17–19]. Song Z et al. used the FAERS database to evaluate hematologic toxicities of tisa-cel and axi-cel, comparing their differences and finding that hemophagocytic lymphohistiocytosis and disseminated intravascular coagulation were underestimated in adverse events [17]. However, their study only assessed tisa-cel and axi-cel, without investigating other marketed CAR-T products. Therefore, there is still a lack of comprehensive research and summary of CAR-T-related hematologic and lymphatic system AEs, and the actual clinical and epidemiological impact of these adverse events can be better assessed in real-world data than in registration trials.

The purpose of this study is to conduct statistical analyses of hematologic and lymphatic system AEs based on CAR-T reports in the FAERS database, perform disproportionality analysis to identify hematologic and lymphatic system adverse reactions, and evaluate and compare the relationships between different CAR-T therapies and hematologic and lymphatic system AEs. We also assessed fatal adverse events related to hematologic and lymphatic systems associated with various CAR-T products. This study aims to provide an in-depth and comprehensive understanding of CAR-T-related hematologic and lymphatic system AEs and offer useful references for clinical practice.

Methods

Data source

We conducted a pharmacovigilance study on hematologic and lymphatic system adverse events (AEs) associated with CAR-T therapy based on the FDA Adverse Event Reporting System (FAERS) database. The FAERS database collects adverse event reports from healthcare professionals, patients, and manufacturers worldwide, including adverse event reports, medication error reports, and product quality complaints leading to adverse events submitted to the FDA. These data are publicly accessible [20].

CAR-T cell therapies, including anti-CD19 cells (tisacel, axi-cel, brexu-cel, liso-cel) and anti-BCMA cells (idecel and cilta-cel), were used as keywords by both brand and generic names to extract CAR-T report data from the FAERS database from August 1, 2017, to December 31, 2023. The selected role_code was "PS" (Primary Suspect). Additionally, adverse reactions reported in the FAERS database are coded according to the Preferred Terms (PT) in the Medical Dictionary for Regulatory Activities (MedDRA). Therefore, hematologic and lymphatic system AEs were coded using MedDRA PTs.

Data processing procedure

We performed deduplication of CAR-T reports obtained from the FAERS database. The detailed screening process is shown in Fig. 1. When the CASE ID was identical, the last FDA_DT was selected. When both CASE ID and FDA_DT were identical, the entry with the larger PRIMARY_ID value was chosen, as per the FAERS user guide [20]. Reports with identical values for fields such as gender, age, country, event date, adverse reactions, and indications were also identified as duplicate reports. We further screened different CAR-T treatment strategies based on adverse reaction reports, distinguishing between anti-CD19 cell and anti-BCMA cell reports. After the above deduplication steps and data screening,

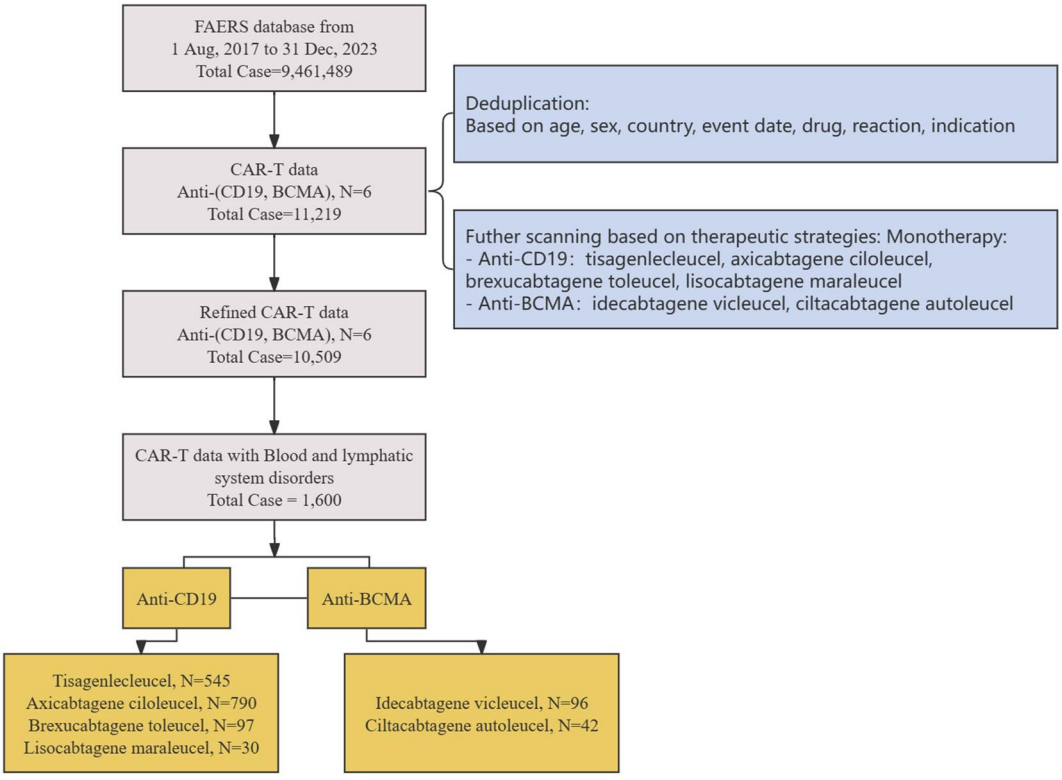

Fig. 1 Flowchart of the study analysis process. Detailed description of the selection process for CAR-T hematologic and lymphatic system adverse events (AEs) from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS)

we obtained the final individual case safety reports of overall adverse events in patients receiving CAR-T therapy from the FAERS database for further analysis ($N = 10,509$).

Signal mining

In the context of pharmacovigilance research, disproportionality analysis methods are primarily used as tools to evaluate potential associations between specific adverse events and particular drugs [21]. Based on the core principles and the advantages and disadvantages of various disproportionality analysis methods [22, 23], we used the Reporting Odds Ratio (ROR) and Bayesian Confidence Propagation Neural Network (known as Information Component (IC)) to detect potential hematologic and lymphatic system AEs in overall or specific CAR-T therapies. A hematologic and lymphatic system adverse event signal was considered valid and highly associated with CAR-T therapy if the number of reports for the hematologic and lymphatic system AE was no less than 3, the lower limit of the 95% confidence interval (CI) of ROR (ROR025) exceeded 1, and the lower limit of the 95% CI of IC (IC025) exceeded 0. Overall, PTs of hematologic and lymphatic disorders meeting these criteria were defined as CAR-T-related adverse events. Reports with CAR-T-related adverse events were selected for further analysis ($N = 1,600$).

Statistical analysis

In addition to signal mining at the PT level, we also compared different CAR-T products. Log-rank tests were performed to compare differences in time to onset between different groups. Time to onset was calculated by subtracting the event start date from the therapy start date, and cumulative distribution curves were used to present event onset information for different groups [24]. Furthermore, the proportion of deaths for different CAR-T products and PTs was calculated. LASSO regression analysis with K-fold cross-validation was employed to select statistically significant PTs associated with mortality. All statistical analyses were performed using R software (version 4.4.0) and Python (version 3.11.7).

Results

Descriptive analysis

We first investigated the occurrence of hematologic and lymphatic system adverse events (AEs) in patients receiving CAR-T therapy from the FAERS database between August 1, 2017, and December 31, 2023. The study design is illustrated in Fig. 1. After excluding irrelevant or duplicate cases, we obtained statistics on hematologic and lymphatic system adverse reactions in patients receiving CAR-T therapy. Among all CAR-T reports, hematologic and lymphatic system AEs accounted for 15.2% (1,600/10,509) of total adverse reactions. The incidence of hematologic and lymphatic system AEs also varied across different CAR-T treatment strategies (Fig. 2). Tisagenlecleucel had the highest incidence of hematologic and lymphatic system AEs (19.9%), while Ciltacabtagene autoleucel had the lowest (5.3%). The incidence of hematologic and lymphatic system AEs was lower in anti-BCMA treatments compared to anti-CD19 treatments (10.9% and 13.8%, respectively).

After screening CAR-T reports in the FAERS database, we obtained cases of CAR-T-related hematologic and lymphatic system AEs ($N = 1,600$) and statistically described the clinical characteristics of these cases (Table 1). The majority of reported cases were male ($N = 843$, 52.7%). The median age of patients was 57 years (interquartile range [IQR] 32–67). Using 18 and 65 years as cut-off points, we divided patients into three different age groups, with the majority of patients being under 65

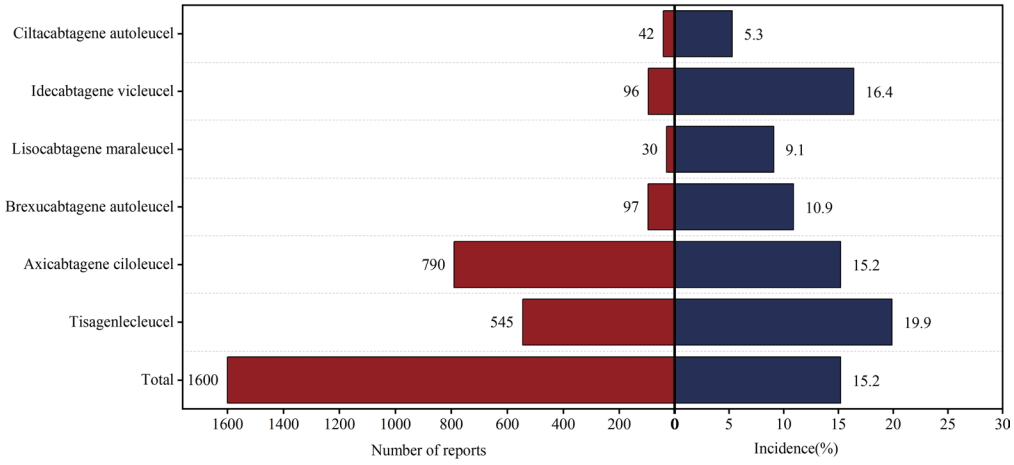

Fig. 2 Statistical data on the incidence of hematologic and lymphatic system adverse events (AEs) in CAR-T reports from the FDA Adverse Event Reporting System (FAERS) database

Table 1 Baseline characteristics of patients with hematologic and lymphatic system adverse events related to chimeric antigen receptor T-Cell therapy

Clinical characteristics	Tisagenlecleucel (*N* = 545)	Axicabtagene ciloleucel (*N* = 790)	Brexucabtagene toleucel (*N* = 97)	Lisocabtagene maraleucel (*N* = 30)	Idecabtagene vicleucel *N*=(96)	Ciltacabtagene autoleucel (*N* = 42)	Total (*N* = 1,600)
Gender							
Female	202(37.1%)	302(38.2%)	23(23.7%)	13(43.3%)	42(43.8%)	15(35.7%)	597(37.3%)
Male	296(54.3%)	404(51.1%)	72(74.2%)	17(56.7%)	40(41.7%)	14(33.3%)	843(52.7%)
Missing	47(8.6%)	84(10.6%)	2(2.1%)	0(0%)	14(14.6%)	13(31.0%)	160(10.0%)
Age in years, median(IQR)	21(12–58)	60(49–67)	63(55.75–69.25)	65.5(56.5–70)	66(62–72)	58.5(54.25-66)	57(32–67)
Age group							
< 18 years	189(34.7%)	2(0.3%)	1(1.0%)	0(0%)	0(0%)	0(0%)	192(12.0%)
18–65 years	174(31.9%)	423(53.5%)	41(42.3%)	14(46.7%)	29(30.2%)	15(35.7%)	696(43.5%)
≥ 65 years	82(15.0%)	221(28.0%)	38(39.2%)	16(53.3%)	42(43.8%)	7(16.7%)	406(25.4%)
Missing	100(18.3%)	144(18.2%)	17(17.5%)	0(0%)	25(26.0%)	20(47.6%)	306(19.1%)
Country							
US	355(65.1%)	366(46.3%)	54(55.7%)	17(56.7%)	55(57.3%)	34(81.0%)	881(55.1%)
JP	31(5.7%)	2(0.3%)	0(0%)	12(40.0%)	4(4.2%)	0(0%)	49(3.1%)
AU	26(4.8%)	6(0.8%)	0(0%)	0(0%)	0(0%)	1(2.4%)	33(2.1%)
FR	26(4.8%)	73(9.2%)	13(13.4%)	0(0%)	21(21.9%)	4(9.5%)	137(8.6%)
ES	18(3.3%)	67(8.5%)	2(2.1%)	0(0%)	0(0%)	2(4.8%)	89(5.6%)
CN	0(0%)	99(12.5%)	2(2.1%)	0(0%)	0(0%)	1(2.4%)	102(6.4%)
DE	11(2.0%)	57(7.2%)	6(6.2%)	0(0%)	2(2.1%)	0(0%)	76(4.8%)
IT	5(0.9%)	29(3.7%)	6(6.2%)	0(0%)	0(0%)	0(0%)	40(2.5%)
Other country	64(11.7%)	91(11.5%)	14(14.4%)	1(3.3%)	14(14.6%)	0(0%)	184(11.5%)
Missing	9(1.7%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	9(0.6%)
Reporter type							
Healthcare professional	466(85.5%)	725(91.8%)	88(90.7%)	28(93.3%)	76(79.2%)	31(73.8%)	1414(88.4%)
Consumer	70(12.8%)	42(5.3%)	1(1.0%)	0(0%)	15(15.6%)	8(19.0%)	136(8.5%)
Missing	9(1.7%)	23(2.9%)	8(8.2%)	2(6.7%)	5(5.2%)	3(7.1%)	50(3.1%)
Outcome							
Death	98(18.0%)	110(13.9%)	18(18.6%)	8(26.7%)	5(5.2%)	5(11.9%)	244(15.3%)
Disability	1(0.2%)	6(0.8%)	2(2.1%)	0(0%)	2(2.1%)	0(0%)	11(0.7%)
Hospitalization	115(21.1%)	218(27.6%)	34(35.1%)	8(26.7%)	21(21.9%)	11(26.2%)	407(25.4%)
Life-threatening	46(8.4%)	23(2.9%)	3(3.1%)	1(3.3%)	1(1.0%)	1(2.4%)	75(4.7%)
Other events	277(50.8%)	411(52.0%)	39(40.2%)	11(36.7%)	66(68.8%)	24(57.1%)	828(51.8%)
Missing	8(1.5%)	22(2.8%)	1(1.0%)	2(6.7%)	1(1.0%)	1(2.4%)	35(2.2%)

years old (*N* = 888, 55.5%). Most case reports came from the United States (*N* = 881, 55.1%), and cases with fatal outcomes accounted for 15.3% (224/1,600).

Hematologic and lymphatic system AEs related to CAR-T therapy

We compiled statistics on the categories and case numbers of hematologic and lymphatic system AEs in CAR-T reports (Supplementary Table S1). The five most common types of hematologic and lymphatic system AEs were neutropenia (*N* = 375, 16.0%), cytopenia (*N* = 263, 11.2%), pancytopenia (*N* = 261, 11.2%), anemia (*N* = 248, 10.6%), and febrile neutropenia (*N* = 243, 10.4%). Cytopenia (*N* = 129, 14.4%), neutropenia (*N* = 224, 20.8%), pancytopenia (*N* = 26, 20.6%), anemia (*N* = 9, 20.5%), anemia (*N* = 25, 17.7%), and neutropenia (*N* = 12, 21.1%) were the most frequently reported hematologic and lymphatic system AEs for tisa-cel, axi-cel, brexu-cel, liso-cel, ide-cel, and cilta-cel, respectively.

Furthermore, after filtering based on our valid signal criteria, we identified different hematologic and lymphatic system AEs associated with various CAR-T therapies (Supplementary Table S2). We identified a total of 25 CAR-T-related signals, with their categories and report numbers shown in Fig. 3A and B. For tisa-cel, 19 signals were significant, with B-cell aplasia being the AE with the strongest signal (ROR025 = 1054.56, IC025 = 4.74). For axi-cel, 16 signals were significant, with cytopenia being the AE with the strongest signal (ROR025 = 17.27, IC025 = 3.81). For brexu-cel, 7 signals were significant, with hypofibrinogenemia being the AE with the strongest signal (ROR025 = 100.18, IC025 = 2.46). For liso-cel,

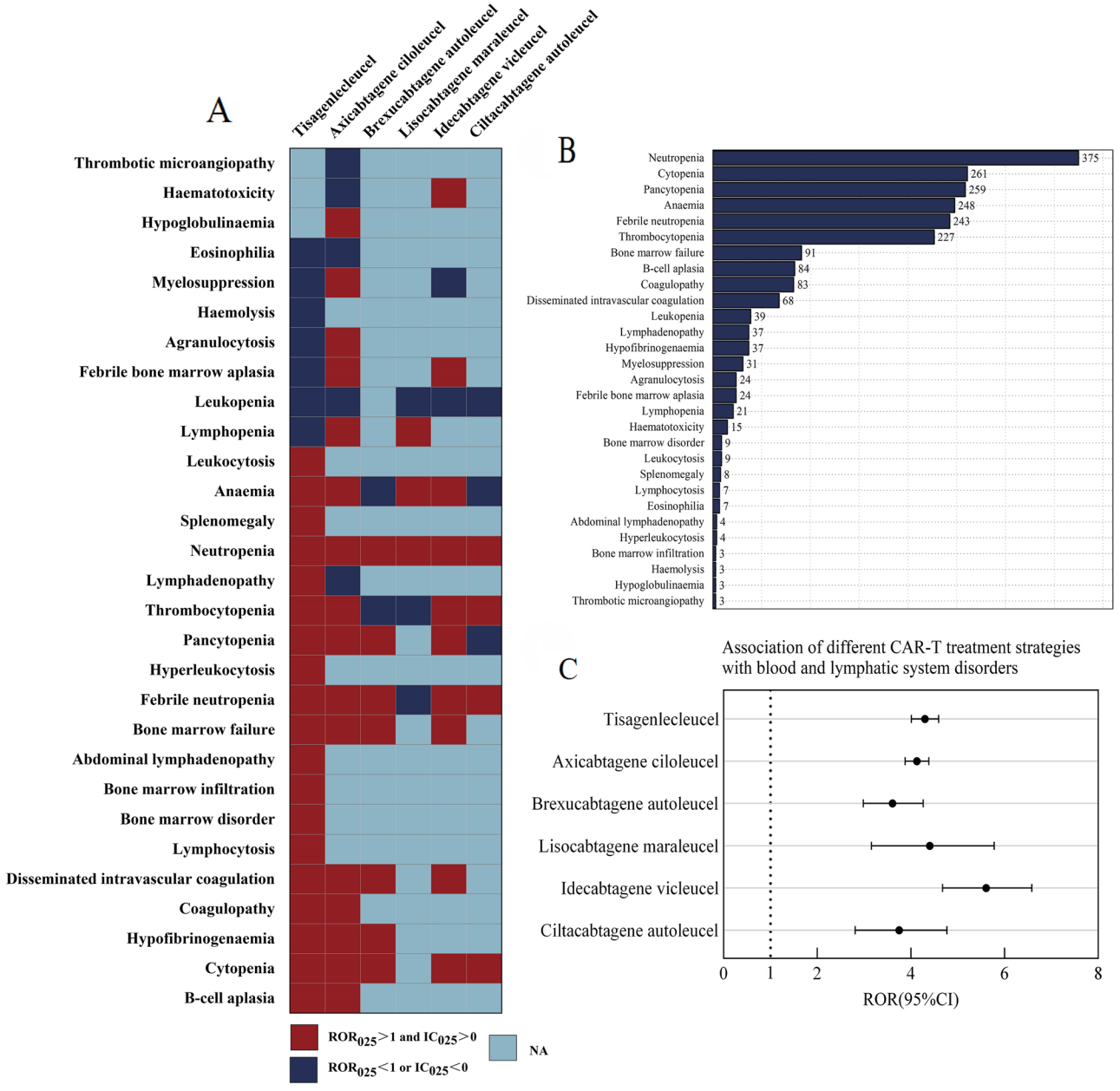

Fig. 3 Hematologic and lymphatic system adverse events (AEs) in CAR-T reports from the FDA Adverse Event Reporting System (FAERS) database. **A**) Heatmap showing ROR025 and IC025 for 29 hematologic and lymphatic system AEs (with at least 3 reports) under different CAR-T treatment strategies in the FAERS database. **B**) Bar chart displaying the number of reports for 29 hematologic and lymphatic system AEs. **C**) Forest plot illustrating the signal values for hematologic and lymphatic system AEs associated with different CAR-T therapies

only 3 signals were significant, with anemia being the AE with the strongest signal (ROR025 = 1.87, IC025 = 0.59). For ide-cel, 10 signals were significant, with febrile bone marrow aplasia being the AE with the strongest signal (ROR025 = 55.32, IC025 = 2.70). For cilta-cel, only 4 signals were significant, with cytopenia being the AE with the strongest signal (ROR025 = 7.18, IC025 = 1.42).

Based on the market launch times of different CAR-T products and using FAERS database data from corresponding time periods as background, we recalculated the hematologic and lymphatic system AEs related to different CAR-T products (Fig. 3C and Supplementary Table S3). Overall, CAR-T therapy was significantly associated with the occurrence of CAR-T-related hematologic and lymphatic system AEs. However, differences existed among different CAR-T products. Treatment with ide-cel was most significantly associated with the occurrence of CAR-T-related hematologic and lymphatic system AEs, with the highest signal values

(ROR025 = 4.68, IC025 = 2.10). Additionally, cilta-cel had the lowest signal values (ROR025 = 2.81, IC025 = 1.38).

We used the upset plot to illustrate the co-occurrence of hematological and lymphatic adverse events of different CAR-T products with adverse events such as CRS, HLH and infection (Supplementary Figure S3). The results show that the average proportion of hematological adverse events (AEs) that occur solely due to CAR-T drugs is no more than 40%, and hematological AEs often overlap with CRS.

Time to onset analysis

The time to onset of hematologic and lymphatic system AEs associated with different CAR-T products is shown in Fig. 4. There were significant differences in the time from infusion to the onset of hematologic and lymphatic system AEs among different CAR-T therapies ($P < 0.0001$) (Fig. 4A). Compared to other CAR-T products, ide-cel had a faster and shorter time to onset of hematologic and lymphatic system AEs, with a median time to onset of 1 day (IQR: 0–4 days). The cilta-cel group had the highest median time to onset at 8.5 days (IQR: 6-15.5 days). Most hematologic and lymphatic system AEs occurred within 10 days after CAR-T infusion. The median time to onset in the fatal group was significantly longer than in the non-fatal group (days: 5 vs. 2, $P = 0.0006$) (Fig. 4B).

Deaths due to blood and lymphatic system disorders associated with CAR-T

The incidence rates and mortality rates of hematological and lymphatic system adverse events (AEs) related to CAR-T products at different times are shown in the figures (Supplementary Figure S1 and Supplementary Figure S2). The trends of the number and incidence of adverse events are not completely consistent. The incidence rate was higher in the year of drug approval, and then the number of adverse reactions increased but the incidence rate decreased. The trends of mortality rates varied among different products. For most drugs, the mortality rate was higher at the beginning and then decreased. To better understand the clinical characteristics of hematologic and lymphatic system AEs and detect highly lethal hematologic and lymphatic system AEs, we further analyzed the prognosis of CAR-T-related hematologic and lymphatic system AEs. We assessed the proportion of deaths due to hematologic and lymphatic system AEs after treatment with different CAR-T products (Fig. 5A and B, and Supplementary Table S4). Among cases with CAR-T-related hematologic and lymphatic system AEs, 15.3% were associated with death. Although the occurrence of CAR-T-related hematologic and lymphatic system AEs may not be the direct cause of death, analysis of fatal outcomes may provide clues for improving patient prognosis. Results showed that lisocel had the highest mortality rate (26.7%), while ide-cel had the lowest (5.2%). Figure 5A shows that compared to other CAR-T products, axi-cel treatment had higher proportions of deaths due to coagulation disorders, disseminated intravascular coagulation, febrile neutropenia, lymphopenia, febrile bone marrow aplasia, agranulocytosis, and bone marrow suppression. Brexu-cel treatment had higher proportions of deaths due to cytopenia and

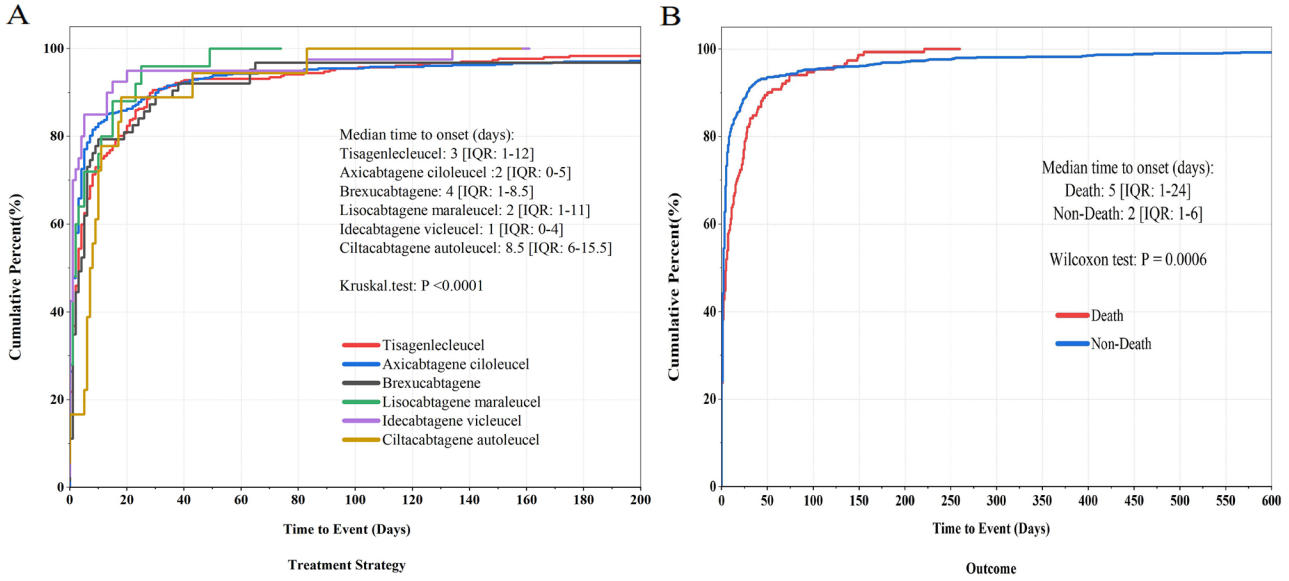

Fig. 4 Time to onset of CAR-T-related hematologic and lymphatic system adverse events (AEs). **A**) Cumulative distribution curves showing the time to onset of related hematologic and lymphatic system AEs under different CAR-T treatment strategies, with statistical testing performed using the non-parametric Kruskal-Wallis rank-sum test. **B**) Cumulative distribution curves showing the time to onset of related hematologic and lymphatic system AEs in fatal and non-fatal groups, with statistical testing performed using the non-parametric Wilcoxon rank-sum test

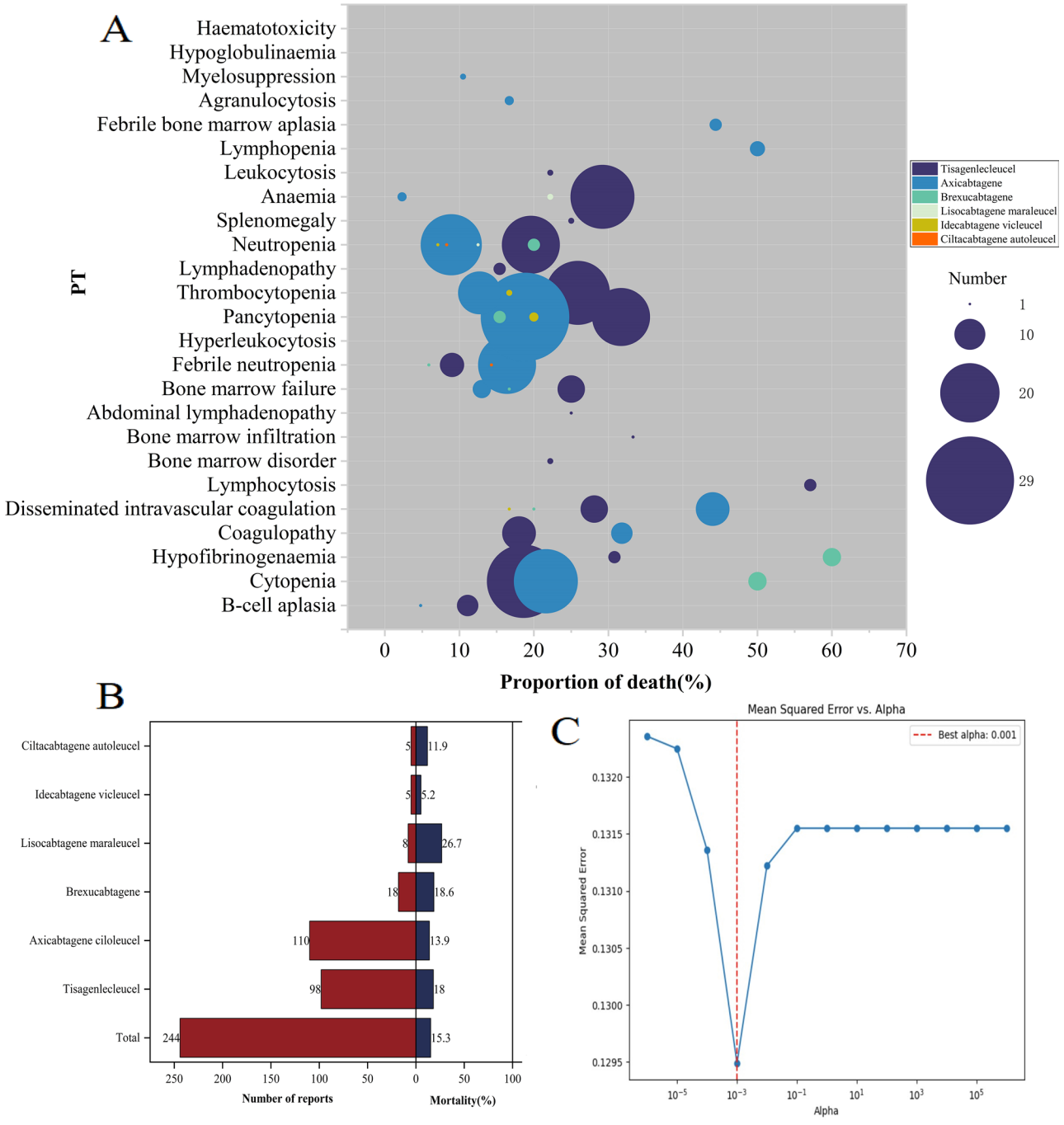

Fig. 5 Assessment of various hematologic and lymphatic system adverse events (AEs) associated with mortality after CAR-T therapy. **A**) Number and proportion of fatal reports for hematologic and lymphatic system AEs following treatment with different CAR-T products. **B**) Number of fatal reports and mortality rates for hematologic and lymphatic system AEs across different CAR-T products. **C**) K-fold cross-validation for selecting the optimal number of K-folds and Alpha parameter for LASSO regression

Table 2 Death-Related hematologic and lymphatic system adverse events selected from K-Fold Cross-Validation LASSO regression

PT	Coefficient(S7)
Agranulocytosis	0.06
Anaemia	-0.07
B-cell aplasia	-0.01
Coagulopathy	0.07
Cytopenia	0.05
Disseminated intravascular coagulation	0.15
Febrile neutropenia	-0.04
Hypofibrinogenaemia	0.09
Lymphadenopathy	0.03
Lymphocytosis	0.04
Lymphopenia	0.07
Neutropenia	-0.02
Pancytopenia	0.09
Splenic haemorrhage	0.23
Thrombocytopenia	0.02

S7 are co-efficients of PT selected from 7-fold cross-validation LASSO regression

hypofibrinogenemia. For the remaining 13 hematologic and lymphatic system AE signals, tisa-cel had higher proportions of deaths.

Additionally, we conducted K-fold cross-validation LASSO regression analysis to identify hematologic and lymphatic system AEs closely associated with mortality (Fig. 5C). Fifteen hematologic and lymphatic system AEs were closely associated with death in patients treated with CAR-T, including splenic hemorrhage, disseminated intravascular coagulation, and pancytopenia (Table 2).

Discussion

Although adverse reactions related to CAR-T therapy have been reported and studied in clinical trials, there is a lack of comprehensive research on associated hematologic and lymphatic adverse events (AEs). This study is a pharmacovigilance investigation of CAR-T-related hematologic and lymphatic AEs based on real-world data from the FAERS database. Using the FAERS database for a specific time period as a comparison, we identified hematologic and lymphatic AEs significantly associated with CAR-T therapy through disproportionality analysis, demonstrated the association between CAR-T and hematologic and lymphatic AEs, and explored the clinical characteristics related to specific CAR-T products. Our study is the largest post-marketing study of CAR-T-related hematologic and lymphatic AEs in a real-world setting to date.

Hematologic and lymphatic AEs are common adverse reactions associated with CAR-T therapy. The FAERS database shows that 15.2% of reports involving CAR-T treatment experienced hematologic and lymphatic AEs. As anti-CD19 CAR-T was approved earlier than anti-BCMA CAR-T, most reports were from patients receiving anti-CD19 CAR-T treatment ($N = 1,462$). The incidence of hematologic and lymphatic AEs was lower in anti-BCMA treatment compared to anti-CD19 treatment (10.9% vs. 13.8%), which may be due to the robust T-cell expansion observed with anti-CD19 CAR-T products [25]. A previous meta-analysis showed that hematologic toxicity was more common in anti-CD19 cases [26], which is consistent with our findings. The occurrence of hematologic and lymphatic AEs is closely related to cytokine release syndrome (CRS), with anti-CD19 CAR-T cells reporting a higher incidence of grade 3 or higher CRS than anti-BCMA CAR-T cells, which may explain the lower incidence of hematologic and lymphatic AEs in anti-BCMA treatment [27]. In another study, anti-BCMA CAR-T treatment for multiple myeloma showed a higher overall response rate compared to non-anti-BCMA CAR-T (e.g., tisagenlecleucel targeting CD19), demonstrating better efficacy [28]. This may provide reasonable evidence for selecting anti-BCMA CAR-T cell therapy.

In further investigation of the clinical characteristics of CAR-T-related hematologic and lymphatic AEs, we observed that patients younger than 65 years were more likely to experience these AEs. Previous studies have also indicated that younger patients are more likely to experience hematologic toxicity [26, 29]. This may be related to more effective immune responses in younger patients after CAR-T infusion. Increasing age may be a risk factor for prolonged grade 3 or higher thrombocytopenia after CAR-T therapy [30]. In terms of different CAR-T products, we found that the number of reports of hematological and lymphatic system adverse events (AEs) after infusion of tisa-cel was lower than that of axi-cel and other products. Bachy and Jacobson also found that the hematological toxicity of axi-cel was significantly more frequent and severe than that of tisa-cel. Therefore, tisa-cel may have more favorable safety profiles [31, 32]. Among all currently marketed CAR-T products, axi-cel and brexu-cel have intracellular domains composed of CD3ζ and CD28 co-stimulatory domains, while other CAR-T therapies have intracellular domains composed of CD3ζ and 4-1BB co-stimulatory domains [33]. Two subgroup analyses indicated that CD28 co-stimulated CAR-T cells are associated with higher acute hematological toxicity (e.g., early-onset cytopenias) compared to 4-1BB co-stimulated products [26, 29]. Consistently, our study found a higher number of reports for CD28 co-stimulated CAR-T products, likely reflecting their propensity for rapid T-cell expansion and cytokine-driven myelosuppression. However, 4-1BB co-stimulated CAR-Ts (e.g., tisa-cel) may exhibit delayed toxicity due to prolonged cellular persistence, as observed in other studies [17]. A study found that the incidence of long-term hematological toxicity (e.g., prolonged cytopenias) after infusion of tisagenlecleucel (4-1BB co-stimulated) was significantly

higher than that of axicabtagene (CD28 co-stimulated) [17]. This discrepancy may be explained by the prolonged persistence of 4-1BB co-stimulated CAR-T cells, which increases the risk of delayed or chronic hematological AEs. In contrast, CD28 co-stimulated products (e.g., axi-cel) are associated with higher acute hematological toxicity due to rapid T-cell expansion and cytokine release. CD28 co-stimulated CAR-Ts (e.g., axi-cel, brexu-cel) are associated with rapid T-cell expansion and intense cytokine release, which may drive acute hematologic toxicity (e.g., early-onset cytopenias, CRS-related myelosuppression). In contrast, 4-1BB co-stimulated CAR-Ts (e.g., tisa-cel, liso-cel) exhibit prolonged persistence, which could contribute to delayed or chronic AEs (e.g., prolonged B-cell aplasia). However, the sample sizes for different CAR-T products were relatively small, and conclusions related to factors affecting CAR-T-related hematologic and lymphatic AEs need to be further validated through larger-scale studies or clinical trials.

Our study identified hematologic and lymphatic AEs associated with CAR-T based on real-world data. The top ten hematologic and lymphatic AEs reported in CAR-T-related cases include neutropenia, cytopenia, pancytopenia, anemia, febrile neutropenia, thrombocytopenia, bone marrow failure, B-cell aplasia, coagulopathy, and disseminated intravascular coagulation (Supplementary Table S1). This is close to the results of CAR-T-related clinical trials and post-marketing studies, which further demonstrates the reliability of our study [4, 13–17]. Hematologic and lymphatic toxicities observed in clinical trials for CAR-T mainly include cytopenias (neutropenia, thrombocytopenia, leukopenia, anemia, or any combination of these symptoms), B-cell aplasia, and coagulopathy. However, there are fewer reports of pancytopenia, bone marrow failure, B-cell aplasia, and disseminated intravascular coagulation, indicating that these hematologic and lymphatic AEs have been largely underestimated in clinical trials. This may be related to the strict inclusion criteria and limited number of participants in clinical trial data [4, 34].

Furthermore, we found that hematologic and lymphatic AEs differ among different CAR-T products (Supplementary Table S2 and Fig. 3A). Cytopenia, represented by neutropenia, is the most common hematologic and lymphatic toxicity of CAR-T, which is consistent with previous studies [29]. For patients receiving tisa-cel treatment, cytopenia had the highest incidence of AEs, which is consistent with clinical trials [34], and B-cell aplasia was the AE with the most significant signal. Studies have found that when tisa-cel is used in ALL patients, the incidence of cytopenia tends to be higher, which may be related to bone marrow infiltration and intensive prior treatment in ALL patients [29]. Due to the on-target off-tumor effect of CD19-directed CAR-T cells on normal B cells, B-cell aplasia is an expected toxicity after CD19-directed CAR-T cell therapy [35], which our study also validates. We did not find reports of B-cell aplasia in BCMA-directed CAR-T. B-cell aplasia was more common in patients receiving tisa-cel treatment than in other patients, possibly due to the longer duration of co-stimulation with tisa-cel, leading to longer CAR-T persistence, which is more likely to cause off-target effects [17]. Patients can receive intravenous immunoglobulin to address this issue [36].

Neutropenia was the most commonly reported hematologic and lymphatic AE for axi-cel, which is also consistent with clinical trial results [17]. The higher incidence of neutropenia in axi-cel patients may reflect the higher dose of myelosuppressive chemotherapy used during lymphocyte depletion [37]. Pancytopenia was the most commonly reported hematologic and lymphatic AE for brexu-cel, and brexu-cel had the highest reporting rate of pancytopenia compared to other CAR-T products. Pancytopenia is a hallmark of highly inflammatory conditions such as hemophagocytic lymphohistiocytosis (HLH)/secondary macrophage activation syndrome and septic shock, and cannot be recovered through growth factor support [38, 39]. Therefore, prevention of pancytopenia is essential in patients receiving brexu-cel treatment. Additionally, we found that products with CD28 co-stimulatory domains had significantly higher incidence rates of pancytopenia than those with 4-1BB domains. Previous studies have shown that products with CD28 domains also tend to have more frequent occurrences of lymphopenia and febrile neutropenia, which our study also found. This may be due to CAR-T cells with CD28 domains exhibiting higher rates of CRS [17, 26]. This finding suggests that products with 4-1BB domains may be more suitable for patients at high risk of HLH, such as those with HLH-related genetic features [17, 40]. Anemia was the most reported hematologic and lymphatic AE for liso-cel and ide-cel. Products with CD28 co-stimulatory domains had a higher incidence of anemia than those with 4-1BB domains [26], which differs from the incidence rates found in our study, but we found that products with CD28 co-stimulatory domains had more reports of anemia than those with 4-1BB domains.

The hematologic and lymphatic toxicities of anti-CD19 CAR-T products and anti-BCMA CAR-T products also differ. Bone marrow failure and disseminated intravascular coagulation are hematologic and lymphatic toxicities associated with CAR-T that are underestimated in clinical practice. Anti-CD19 CAR-T products had higher incidence rates and signal strengths for bone marrow failure and disseminated intravascular coagulation than anti-BCMA CAR-T products (Supplementary Table S2). Disseminated intravascular coagulation

is a rapidly progressing and life-threatening hematologic and lymphatic AE that needs to be monitored, and there is a strong correlation between disseminated intravascular coagulation and CRS [38, 41, 42]. Therefore, anti-BCMA CAR-T products may reduce the risk of disseminated intravascular coagulation. Conversely, anti-CD19 CAR-T products had lower incidence rates and signal strengths for hemotoxicity and leukopenia than anti-BCMA CAR-T products. This may be because the risk of leukopenia seems to increase in subgroups with lower male proportions compared to subgroups with higher male proportions [29]. Anti-BCMA CAR-T products have a lower proportion of males compared to anti-CD19 CAR-T products. These findings suggest that we can optimize the selection of CAR-T products based on each patient's baseline characteristics before treatment, thereby reducing the risk of hematologic and lymphatic toxicities.

There were significant differences in the onset time of hematologic and lymphatic AEs among different CAR-T products. We found that most hematologic and lymphatic AEs occurred within 10 days after CAR-T infusion. Other studies have also shown that CAR-T hematologic and lymphatic AEs occur early in the course of CAR-T treatment [10, 43]. Compared to other CAR-T products, ide-cel had a faster and shorter onset time, while the cilta-cel group had the highest median onset time. Wesson W's study found that the median onset day for ide-cel was significantly shorter than that for cilta-cel [44], which is consistent with our findings. Furthermore, Wang J et al. [45] reported that hematologic toxicities often occur 5 days after preconditioning. It has been observed that cytopenia, leukopenia, and lymphopenia are more common in patients who have undergone intensive preconditioning [29]. Two other studies evaluating ide-cel and cilta-cel both reported a significantly higher proportion of hematologic adverse events in patients who had undergone intensive preconditioning [7, 46]. The preconditioning regimen is an important component of the CAR-T treatment procedure, and generally, preconditioning chemotherapy is administered 3–5 days before infusion [47]. Preconditioning chemotherapy intensity and timing are known to affect CAR-T expansion, cytokine release, and hematologic toxicity. For example, high-dose fludarabine may exacerbate prolonged cytopenias. Unfortunately, FAERS does not capture detailed lymphodepletion data, limiting our ability to analyze these relationships. Future studies with standardized preconditioning protocols are needed to isolate CAR-T-specific toxicity profiles. These results suggest that we need to be aware of hematologic and lymphatic toxicities shortly after starting CAR-T treatment, especially after preconditioning.

In the LASSO regression analysis, 15 hematologic and lymphatic AEs were associated with death in patients receiving CAR-T treatment. Except for bone marrow failure, the top ten hematologic adverse events by number of reports were all associated with death. AEs with higher correlations included splenic hemorrhage, disseminated intravascular coagulation, and pancytopenia. Splenic hemorrhage is a bleeding event, and studies have shown that bleeding events after CAR-T cell therapy are likely to lead to patient death [1, 48, 49]. A post-marketing study also found that splenic hemorrhage was a highly death-related adverse event in tisa-cel and axi-cel, with a mortality rate of 100% in tisa-cel [17], but splenic hemorrhage is not a risk signal for CAR-T adverse events and may be related to the disease itself. Disseminated intravascular coagulation is a life-threatening hematologic AE that needs to be monitored [17]. Although the pathophysiology of CAR-T-related disseminated intravascular coagulation is unclear, many studies speculate that patients with severe CRS have a higher incidence of disseminated intravascular coagulation [42, 50]. Disseminated intravascular coagulation generally develops from coagulopathy, and early management of coagulopathy may help prevent CRS-related deaths [51]. Pancytopenia is a severe, prolonged hematologic and lymphatic adverse reaction that cannot be recovered through growth factor support [39]. Recent studies have revealed that persistent pancytopenia is associated with infectious complications [52]. Severe infectious complications have become the number one cause of long-term non-relapse mortality after CAR-T cell therapy, and infectious complications secondary to long-term severe pancytopenia affect the non-relapse mortality rate after CAR-T cell therapy [12, 39]. Some studies have also pointed out that cytopenia increases the relapse and mortality rates after CAR-T treatment, which is consistent with our findings [43]. While our study identified pancytopenia as a key mortality-associated AE, its overlap with cytopenias and its frequent co-occurrence with CRS/HLH (Supplementary Figure S3) suggest that these events may be secondary to systemic inflammatory responses. Thus, these events underscores the need for prospective studies to dissect causal relationships. Additionally, we found that anti-CD19 CAR-T products had higher mortality rates related to hematologic and lymphatic AEs than anti-BCMA CAR-T products, which may be related to more reports of death-related adverse events such as disseminated intravascular coagulation, B-cell aplasia, and hypofibrinogenemia. Studies have shown that adverse events such as B-cell aplasia further increase the risk of infection as on-target/off-tumor toxicity of CD19-targeted CAR-T cell therapy [53]. Therefore, early identification and intervention of these hematologic and lymphatic AEs with higher mortality rates are crucial for effectively reducing the incidence of serious adverse events and mortality.

This study has several limitations. First, FAERS is a voluntary reporting system, and not all reports of adverse reactions are collected. The number of patients receiving CAR-T treatment has not been reported, lacking denominator data. Therefore, we cannot obtain a causal relationship between CAR-T and hematologic and lymphatic AEs, nor can we calculate the true incidence of CAR-T-related hematologic and lymphatic AEs, and conclusions should be interpreted as hypothesis-generating. Additionally, each report lacks specific time of death, which hinders our further risk analysis of the onset time of CAR-T-related hematologic and lymphatic AEs. Second, there is some overlap in toxicity between cytopenia and anemia, thrombocytopenia, and neutropenia, making it difficult to completely separate them. Third, spontaneously reported data are generally not as reliable as data collected in clinical trials and cohort studies, and comparisons between different CAR-T products are limited by potentially imbalanced characteristics of patient populations. The later approval of BCMA CAR-T therapies (e.g., ide-cel and cilta-cel) resulted in fewer reported cases compared to CD19 CAR-Ts, potentially underestimating their hematologic toxicity profiles. Comparisons between these groups should be interpreted cautiously. The absence of preconditioning regimen details in FAERS prevents adjustment for their confounding effects on AE outcomes. This underscores the need for prospective registries with comprehensive clinical data to validate our findings. Despite the limitations of FAERS, our study results reveal fundamental aspects of CAR-T-related hematologic and lymphatic events and may provide a basis for subsequent rigorous prospective studies.

Based on real-world data from the FAERS database, we analyzed hematologic and lymphatic AEs associated with CAR-T products and compared the differences among various CAR-T products. Hematologic and lymphatic AEs are more closely associated with anti-CD19 CAR-T and CAR-T containing CD28 domains. Splenic hemorrhage, disseminated intravascular coagulation, and pancytopenia are hematologic and lymphatic AEs that are less frequently reported clinically but highly associated with death. These findings highlight differences in hematologic and lymphatic AE profiles among CAR-T products and provide a foundation for prospective studies to further evaluate their safety profiles in controlled clinical settings.

Supplementary Information

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Supplementary Material 1

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Author contributions
ZZ, LM and LS are responsible for study concept, methodology and software. ZZ, YL and JP are responsible for data curation, and prepared and wrote the original draft. ZZ, QW and CD are responsible for visualization and investigation of data. ZZ and YL are responsible for software and data validation. ZZ, LM and LS wrote, reviewed and edited the paper.

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Data availability
This study was performed on the basis of data from Food and Drug Administration Adverse Event Reporting System (FAERS), a publicly available and anonymized database (https://www.fda.gov/regulatory-information/freedom-information).

Declarations

Ethics approval and consent to participate
Not applicable. FDA Adverse Event Reporting System is a spontaneous reporting system, the publicly available data are anonymized, and therefore, obtaining consent to participate is not applicable. The present pharmacovigilance study was conducted using a public database of spontaneous reports. Given the use of deidentified data, ethical approval was not considered necessary.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-Cell lymphoblastic leukemia. N Engl J Med. 2018;378(5):439–48. https://doi.org/10.1056/NEJMoa1709866.
2. Shah N, Chari A, Scott E, Mezzi K, Usmani SZ. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. Leukemia. 2020;34(4):985–1005. https://doi.org/10.1038/s41375-020-0734-z.
3. Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med. 2022;28(2):325–32. https://doi.org/10.1038/s41591-021-01622-0.
4. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of Axicabtagene Ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. Lancet Oncol. 2019;20(1):31–42. https://doi.org/10.1016/S1470-2045(18)30864-7.
5. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene Maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839–52. https://doi.org/10.1016/S0140-6736(20)31366-0.
6. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-Cell therapy in relapsed or refractory Mantle-Cell lymphoma. N Engl J Med. 2020;382(14):1331–42. https://doi.org/10.1056/NEJMoa1914347.

7. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705–16. https://doi.org/10.1056/NEJMoa2024850.
8. Martin T, Usmani SZ, Berdeja JG, et al. Ciltacabtagene autoleucel, an Anti-B-cell maturation antigen chimeric antigen receptor T-Cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-Year Follow-Up. J Clin Oncol. 2023;41(6):1265–74. https://doi.org/10.1200/JCO.22.00842.
9. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer J. 2021;11(4):69. https://doi.org/10.1038/s41408-021-00459-7. Published 2021 Apr 6.
10. Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. Bone Marrow Transpl. 2019;54(10):1643–50. https://doi.org/10.1038/s41409-019-0487-3.
11. Zhang X, Zhu L, Zhang H, Chen S, Xiao Y. CAR-T cell therapy in hematological malignancies: current opportunities and challenges. Front Immunol. 2022;13:927153. https://doi.org/10.3389/fimmu.2022.927153. Published 2022 Jun 10.
12. Wudhikarn K, Pennisi M, Garcia-Recio M, et al. DLBCL patients treated with CD19 CAR T cells experience a high burden of organ toxicities but low non-relapse mortality. Blood Adv. 2020;4(13):3024–33. https://doi.org/10.1182/bloodadvances.2020001972.
13. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015;385(9967):517–28. https://doi.org/10.1016/S0140-6736(14)61403-3.
14. Logue JM, Zucchetti E, Bachmeier CA, et al. Immune reconstitution and associated infections following Axicabtagene Ciloleucel in relapsed or refractory large B-cell lymphoma. Haematologica. 2021;106(4):978–86. https://doi.org/10.3324/haematol.2019.238634. Published 2021 Apr 1.
15. Schubert ML, Dietrich S, Stilgenbauer S, et al. Feasibility and safety of CD19 chimeric antigen receptor T cell treatment for B cell lymphoma relapse after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transpl. 2020;26(9):1575–80. https://doi.org/10.1016/j.bbmt.2020.04.025.
16. Shi X, Yan L, Shang J, et al. Anti-CD19 and anti-BCMA CAR T cell therapy followed by Lenalidomide maintenance after autologous stem-cell transplantation for high-risk newly diagnosed multiple myeloma. Am J Hematol. 2022;97(5):537–47. https://doi.org/10.1002/ajh.26486.
17. Song Z, Tu D, Tang G, et al. Hemophagocytic lymphohistiocytosis and disseminated intravascular coagulation are underestimated, but fatal adverse events in chimeric antigen receptor T-cell therapy. Haematologica. 2023;108(8):2067–79. https://doi.org/10.3324/haematol.2022.281455. Published 2023 Aug 1.
18. Fusaroli M, Isgrò V, Cutroneo PM, et al. Post-Marketing surveillance of CAR-T-Cell therapies: analysis of the FDA adverse event reporting system (FAERS) database. Drug Saf. 2022;45(8):891–908. https://doi.org/10.1007/s40264-022-01194-z.
19. Gomez-Lumbreras A, Mercadal Vilchez S, Villa-Zapata L, Malone DC, Couriel DR. Chimeric antigen receptor T-cell immunotherapies adverse events reported to FAERS database: focus on cytopenias. Leuk Lymphoma. 2023;64(13):2071–80. https://doi.org/10.1080/10428194.2023.2254430.
20. U.S. Food and Drug Administration. FDA Adverse Event Reporting System (FAERS) Quarterly Data Extract Files. 2023. https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. Accessed 30 May 2024.
21. Caster O, Aoki Y, Gattepaille LM, Grundmark B. Disproportionality analysis for pharmacovigilance signal detection in small databases or subsets: recommendations for limiting False-Positive associations. Drug Saf. 2020;43(5):479–87. https://doi.org/10.1007/s40264-020-00911-w.
22. Ang PS, Chen Z, Chan CL, Tai BC. Data mining spontaneous adverse drug event reports for safety signals in Singapore - a comparison of three different disproportionality measures. Expert Opin Drug Saf. 2016;15(5):583–90. https://doi.org/10.1517/14740338.2016.1167184.
23. Hou Y, Ye X, Wu G, Cheng G, Du X, He J. A comparison of disproportionality analysis methods in National adverse drug reaction databases of China. Expert Opin Drug Saf. 2014;13(7):853–7. https://doi.org/10.1517/14740338.2014.915938.
24. Zhou C, Peng S, Lin A, et al. Psychiatric disorders associated with immune checkpoint inhibitors: a pharmacovigilance analysis of the FDA adverse event reporting system (FAERS) database. EClinicalMedicine. 2023;59:101967. https://doi.org/10.1016/j.eclinm.2023.101967. Published 2023 Apr 21.
25. Maus MV, Alexander S, Bishop MR, et al. Society for immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. J Immunother Cancer. 2020;8(2):e001511. https://doi.org/10.1136/jitc-2020-001511.
26. Luo W, Li C, Zhang Y, et al. Adverse effects in hematologic malignancies treated with chimeric antigen receptor (CAR) T cell therapy: a systematic review and Meta-analysis. BMC Cancer. 2022;22(1):98. https://doi.org/10.1186/s12885-021-09102-x. Published 2022 Jan 24.
27. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-Cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med. 2019;380(18):1726–37. https://doi.org/10.1056/NEJMoa1817226.
28. Yang Q, Li X, Zhang F, Yang Q, Zhou W, Liu J. Efficacy and safety of CAR-T therapy for relapse or refractory multiple myeloma: A systematic review and meta-analysis. Int J Med Sci. 2021;18(8):1786–97. https://doi.org/10.7150/ijms.46811. Published 2021 Feb 18.
29. Xia Y, Zhang J, Li J, et al. Cytopenias following anti-CD19 chimeric antigen receptor (CAR) T cell therapy: a systematic analysis for contributing factors. Ann Med. 2022;54(1):2951–65. https://doi.org/10.1080/07853890.2022.2136748.
30. Thibaud S, Mia M, Van Oekelen O, et al. Comprehensive characterization of prolonged unexplained cytopenias in relapsed/refractory multiple myeloma patients following BCMA-Directed CAR-T cell therapy. Blood. 2022;140(Supplement 1):614–6. https://doi.org/10.1182/blood-2022-165646.
31. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and Axicabtagene Ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med. 2022;28(10):2145–54. https://doi.org/10.1038/s41591-022-01969-y.
32. Jacobson CA, Munoz J, Sun F, et al. Real-World outcomes with chimeric antigen receptor T cell therapies in large B cell lymphoma: A systematic review and Meta-Analysis. Transpl Cell Ther. 2024;30(1):77e. 1-77.e15.
33. Li Y, Ming Y, Fu R et al. The pathogenesis, diagnosis, prevention, and treatment of CAR-T cell therapy-related adverse reactions. Front Pharmacol. 2022;13:950923. Published 2022 Oct 14. https://doi.org/10.3389/fphar.2022.950923
34. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-Cell lymphoma. N Engl J Med. 2019;380(1):45–56. https://doi.org/10.1056/NEJMoa1804980.
35. Schubert ML, Schmitt M, Wang L, et al. Side-effect management of chimeric antigen receptor (CAR) T-cell therapy. Ann Oncol. 2021;32(1):34–48. https://doi.org/10.1016/j.annonc.2020.10.478.
36. Brudno JN, Somerville RP, Shi V, et al. Allogeneic T cells that express an Anti-CD19 chimeric antigen receptor induce remissions of B-Cell malignancies that progress after allogeneic hematopoietic Stem-Cell transplantation without causing Graft-Versus-Host disease. J Clin Oncol. 2016;34(10):1112–21. https://doi.org/10.1200/JCO.2015.64.5929.
37. Rejeski K, Perez A, Sesques P, et al. CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. Blood. 2021;138(24):2499–513. https://doi.org/10.1182/blood.2020010543.
38. Sandler RD, Tattersall RS, Schoemans H, et al. Diagnosis and management of secondary HLH/MAS following HSCT and CAR-T cell therapy in adults; A review of the literature and a survey of practice within EBMT centres on behalf of the autoimmune diseases working party (ADWP) and transplant complications working party (TCWP). Front Immunol. 2020;11:524. https://doi.org/10.3389/fimmu.2020.00524. Published 2020 Mar 31.
39. Rejeski K, Kunz WG, Rudelius M et al. Severe Candida glabrata pancolitis and fatal Aspergillus fumigatus pulmonary infection in the setting of bone marrow aplasia after CD19-directed CAR T-cell therapy - a case report. BMC Infect Dis. 2021;21(1):121. Published 2021 Jan 28. https://doi.org/10.1186/s12879-020-05755-4
40. Tesi B, Lagerstedt-Robinson K, Chiang SC, et al. Targeted high-throughput sequencing for genetic diagnostics of hemophagocytic lymphohistiocytosis. Genome Med. 2015;7:130. https://doi.org/10.1186/s13073-015-0244-1. Published 2015 Dec 18.
41. Cutini I, Puccini B, Fabbri A, et al. Late haemophagocytic lymphohistiocytosis in a patient treated with Axicabtagene Ciloleucel. Transpl Immunol. 2022;75:101719. https://doi.org/10.1016/j.trim.2022.101719.
42. Wang Y, Qi K, Cheng H, et al. Coagulation disorders after chimeric antigen receptor T cell therapy: analysis of 100 patients with relapsed and refractory hematologic malignancies. Biol Blood Marrow Transpl. 2020;26(5):865–75. https://doi.org/10.1016/j.bbmt.2019.11.027.
43. Jain T, Olson TS, Locke FL. How I treat cytopenias after CAR T-cell therapy. Blood. 2023;141(20):2460–9. https://doi.org/10.1182/blood.2022017415.

44. Wesson W, Dima D, Suleman N, et al. Timing of toxicities and Non-relapse mortality following CAR T therapy in myeloma. Transpl Cell Ther Published Online June. 2024;11. https://doi.org/10.1016/j.jtct.2024.06.012.
45. Wang J, Mou N, Yang Z, et al. Efficacy and safety of humanized anti-CD19-CAR-T therapy following intensive lymphodepleting chemotherapy for refractory/relapsed B acute lymphoblastic leukaemia. Br J Haematol. 2020;191(2):212–22. https://doi.org/10.1111/bjh.16623.
46. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study [published correction appears in lancet. 2021;398(10307):1216. Doi: 10.1016/S0140-6736(21)02132-2]. Lancet. 2021;398(10297):314–24. https://doi.org/10.1016/S0140-6736(21)00933-8.
47. Ghorashian S, Kramer AM, Onuoha S, et al. Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. Nat Med. 2019;25(9):1408–14. https://doi.org/10.1038/s41591-019-0549-5.
48. Turtle CJ, Hanafi LA, Berger C, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8 + and CD4 + CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med. 2016;8(355):355ra116. https://doi.org/10.1126/scitranslmed.aaf8621.
49. Wang Y, Zhang WY, Han QW, et al. Effective response and delayed toxicities of refractory advanced diffuse large B-cell lymphoma treated by CD20-directed chimeric antigen receptor-modified T cells. Clin Immunol. 2014;155(2):160–75. https://doi.org/10.1016/j.clim.2014.10.002.
50. Jiang H, Liu L, Guo T, Wu Y, Ai L, Deng J, et al. Improving the safety of CAR-T cell therapy by controlling CRS-related coagulopathy. Ann Hematol. 2019;98(7):1721–32. https://doi.org/10.1007/s00277-019-03685-z.
51. Liu R, Lv Y, Hong F, et al. A comprehensive analysis of coagulopathy during anti-B cell maturation antigen chimeric antigen receptor-T therapy in multiple myeloma, a retrospective study based on LEGEND-2. Hematol Oncol. 2023;41(4):704–17. https://doi.org/10.1002/hon.3155.
52. Kansagra AJ, Frey NV, Bar M, et al. Clinical utilization of chimeric antigen receptor T cells in B cell acute lymphoblastic leukemia: an expert opinion from the European society for blood and marrow transplantation and the American society for blood and marrow transplantation. Biol Blood Marrow Transpl. 2019;25(3):e76–85. https://doi.org/10.1016/j.bbmt.2018.12.068.
53. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood. 2016;127(26):3321–30.

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