Hemophagocytic lymphohistiocytosis and disseminated intravascular coagulation are underestimated, but fatal adverse events in chimeric antigen receptor T-cell therapy

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Abstract

Hematotoxicity is the most common long-term adverse event (AE) after chimeric antigen receptor T-cell (CAR T) therapy. However, patients who receive CAR T therapy in pivotal clinical trials are subjected to restrictive selection criteria, and this means that rare but fatal toxicities are underestimated. Here, we systematically analyzed CAR T-associated hematologic AE using the US Food and Drug Administration Adverse Event Reporting System (FAERS) between January 2017 and December 2021. Disproportionality analyses were performed using reporting odds ratios (ROR) and information component (IC); the lower limit of the ROR and IC 95% confidence interval (CI) (ROR_{025} and IC_{025}) exceeding one and zero was considered significant, respectively. Among the 105,087,611 reports in FAERS, 5,112 CAR T-related hematotoxicity reports were identified. We found 23 significant over-reporting hematologic AE (ROR025 >1) compared to the full database, of which hemophagocytic lymphohistiocytosis (HLH; n=136 [2.7%], ROR_{025} = 21.06), coagulopathy (n=128 [2.5%], ROR_{025} = 10.43), bone marrow failure (n=112 [2.2%], ROR_{025} = 4.88), disseminated intravascular coagulation (DIC; n=99 [1.9%], ROR_{025} = 9.64), and B-cell aplasia (n=98 [1.9%], ROR_{025} = 118.16, all IC_{025} > 0) were highly under-reported AE in clinical trials. Importantly, HLH and DIC led to mortality rates of 69.9% and 59.6%, respectively. Lastly, hematotoxicity-related mortality was 41.43%, and 22 death-related hematologic AE were identified using LASSO regression analysis. These findings could help clinicians in the early detection of those rarely reported but lethal hematologic AE, thus reducing the risk of severe toxicities for CAR T recipients.

Introduction

CD19 chimeric antigen receptor T-cell (CAR T) therapy is a promising treatment for patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL) and large B-cell lymphoma.[1,2] The CD19 CAR T products axicabtagene-ciloleucel (axicabtagene) and tisagenlecleucel have gained wide popularity due to the unprecedented treatment efficacy of hematologic malignancies. For patients with r/r diffuse large B-cell lymphoma, traditional chemotherapy resulted in a poor complete response rate (CR, 7%) and overall survival (OS) of 2 years (20%),[3] while the rate of CR and OS at 2 years exceeded 50% after axicabtagene therapy.[4] Similarly, tisagenlecleucel also contributed to a remarkable CR rate (90%) and 2-year OS rate (73%) in patients with r/r B-ALL.[5]

However, the administration of CD19 CAR T products increases the risk of serious and fatal adverse events (AE). Cytokine release syndrome (CRS) is the most common adverse event caused by rapid activation of the immune system.[6] The incidence of CRS varies from 35% to 93%, depending on the CAR T product used, the tumor burden,

and the CRS grading criteria.[7] Furthermore, hematotoxicity has become the most common long-term AE after CAR T-cell infusion with severe outcomes.[8] The incidence of serious anemia (grade 3) and thrombocytopenia and neutropenia after three weeks of CAR T transfusion has been reported to range from 5% to 17%, 21% to 29%, and 30% to 38%, respectively.[9-12] Meanwhile, 16% patients had prolonged cytopenia for 22 months and had to receive transfusions or growth factor support after CD19 CAR T-cell therapy.[13] Importantly, prolonged neutropenia increases the risk of infectious complications, which are the most common cause of non-relapse mortality (NRM).[2] It is critical to comprehensively understand CAR T-associated hematologic AE, and a systematic safety profile should be evaluated before treating patients, especially given the rapid increase in the use of this revolutionary therapy. Meanwhile, it is helpful to detect and prevent some rare but lethal AE, such as hemophagocytic lymphohistiocytosis (HLH) and disseminated intravascular coagulation (DIC). However, clinical trials are subject to restrictive inclusion criteria and thus include highly selected patients,[4,14] leading to the frequency of hematologic AE, especially some rare AE, being underestimated. Therefore, post-marketing AE reports could help identify the safety profile of new therapies by revealing real-world data and detecting rare but lethal toxicities.

The aim of this study was to extensively evaluate hematologic AE associated with CAR T using the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and to alert clinicians earlier to those rarely reported but severe hematologic toxicities, thus improving the management of CAR T-cell recipients and reducing the risk of lethal hematotoxicity.

Methods

Data sources and study design

This retrospective post-marketing CAR T-cell therapy safety analysis was performed on the basis of data extracted from FAERS between 1 January 2017 and 31 December 2021. In this study, only the adverse reports, including CAR T-associated trade or generic names, such as "AXICABTAGENE," "CILOLEUCEL," "AXICABTAGEN-CILOLEUCEL," "AXI-CEL," "KTE C19," "TISAGENLECLEUCEL," "CTL019," "KYMRIAH," "TISA-CEL" were selected for analysis (see *Online Supplementary Table S1* for details). In particular, all AE in the FAERS database were coded and standardized with reference to the level of preferred term (PT) according to the FDA's Medical Dictionary for Regulatory Activities (MedDRA). Therefore, the hematologic toxicities were coded according to the PT of MedDRA. All datasets in this study can be accessed at: https://www.fda.gov/regulatory-information/freedom-information.

Statistical analysis

Disproportionality analysis methods, including the reporting odds ratio (ROR) and the information component (IC), were used to detect potential hematologic AE in total or specific CAR T products.[15,16] A statistical shrinkage transformation was performed to maintain more robust results,17 and the relative statistical formula is as follows:

$$n_{exp} = (n_{drug} * n_{event})/n_{total}$$

$$ROR = (n_{obe} + 0.5)/(n_{exp} + 0.5)$$

$$IC = \log_2 ((n_{obe} + 0.5)/(n_{exp} + 0.5))$$

n_{exp} and n_{obe} are the numbers of expected and observed drug-adverse event records, respectively. n_{drug} is the number of records of the relevant drugs. Similarly, n_{event} represents the number of associated AE records. n_{total} is the number of drug AE records. In particular, signal detection was only conducted for drug-AE pairs with at least three case records. A statistically significant signal was identified if the lower limit value of the ROR 95% confidence interval (ROR_{025}) exceeded one or the lower bound value of the 95% confidence interval for the IC (IC_{025}) was greater than zero,[15,16] which means target AE or combinations were reported more frequently in the targeted drugs than in the control group.

In addition to classic signal detection at the PT level, signal analysis was also performed in AE of clinical interest based on HLT. Furthermore, we conducted a signal comparison of several variables, including products (tisagenlecleucel *vs.* axicabtagene), sex (male *vs.* female), and age (age <65 *vs.* 65 years). A log-rank test was performed to compare time-to-onset differences in various groups, such as two CAR T products, the top ten frequently reported PT, and six types of HLT. Furthermore, the proportion of deaths was calculated for different PT and HLT. We also performed a LASSO regression analysis to select statistically significant PT associated with death. Finally, the UpSet plot, Venn diagram, and charts were used to explore the potential overlap between different PT, HLT, and CRS, and provide relative indications for prompt treatment. All statistical analyzes were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) and R software (version 4.1.2).

Results

Descriptive analysis

The study design is illustrated in Figure 1. Among the 105,087,611 reports in the FAERS database between 1 January 2017 and 31 December 2021, 43,830 toxicity reports were associated with CAR T therapy (axicabtagene, n=14,464 [33.0%]; tisagenlecleucel, n=29,366 [67.0%]) (Figure 1). Among them, 5,112 reports were hematologic AE, of which 1,494 (29.2%) reports were associated with axicabtagene and 3,618 (70.8%) with tisagenlecleucel. The overall reporting rate for hematologic AE was lower in patients

receiving axicabtagene than in those receiving tisagenlecleucel (10.3% *vs*. 12.3%, respectively). According to (MedDRA,[18] 23 and 36 PT of hematologic AE are associated with axicabtagene and tisagenlecleucel, respectively. In general, reported hematologic AE consistently increased from 2017 to 2020 in CAR T recipients, with a slight decrease in 2021 (Table 1). Hematotoxicity-related mortality was 41.43% (n=2,118), of which the fatality rates were 32.46% (n=485) and 45.14% (n=1,633) after treatment with axicabtagene and tisagenlecleucel, respectively. Among various countries, the United States reported the highest number of hematologic AE (70.54%). Most of the patients who received CAR T therapy were younger than 65 years in both the axicabtagene (n = 729, 66.8%) and tisagenlecleucel (n=2,589, 84.9%) groups, but younger patients (<65 years) had a higher reporting frequency of hematologic AE compared to older patients (≥65 years, ROR=1.33, 95% confidence interval [CI:] 1.23-1.45) (*Online Supplementary Table S2*).

CAR T-therapy-associated hematologic adverse events

In general, the top ten reported hematologic AE after CAR T therapy were cytopenia (n=517, 10.1%), neutropenia (n=463, 9.1%), thrombocytopenia (n=318, 6.2%), febrile neutropenia (n=273, 5.3%), pancytopenia (n=225, 4.4%), hemophagocytic lymphohistiocytosis (HLH, n=136, 2.7%), anemia (n=129, 2.5%), coagulopathy (n=128, 2.5%), bone marrow failure (n=112, 2.2%), and disseminated intravascular coagulation (DIC, n=99, 1.9%) (Table 2 and *Online Supplementary Figure S1*). Furthermore, we identified 23 over-reported hematologic AE (ROR_{025} > 1) (Table 2). For axicabtagene, neutropenia (n=221) was the most frequently over-reported hematologic AE, corresponding to ROR_{025} = 6.47 and IC_{025} = 2.64. Cytopenia (n=427) was the most reported hematologic AE after tisagenlecleucel (ROR_{025} = 66.05, IC_{025} = 5.90). The signal values of the IC025 and ROR_{025} distribution of the top ten reported AE are presented in *Online Supplementary Figure S1*. The strongest signal values of axicabtagene and tisagenlecleucel-associated hematologic AE were HLH (ROR_{025} = 22.77, IC_{025} = 4.42) and B-cell aplasia (ROR_{025} = 104.20, IC_{025} = 6.65), respectively.

To better understand hematologic AE associated with CAR T-cell therapy, hematotoxicity PT were divided into six subgroups based on MedDRA HLT, including bone marrow depression, coagulopathies and bleeding diatheses, hematologic disorders, hemolyses, spleen disorders, and other events (*Online Supplementary Table S3*). Bone marrow depression, coagulopathies and bleeding diatheses, and hematologic disorders were significantly correlated with axicabtagene and tisagenlecleucel (ROR_{025} > 1 and IC_{025} > 0) (*Online Supplementary Table S4*). However, spleen disorders and hemolyses were significantly associated only with tisagenlecleucel and axicabtagene, respectively. Hematologic disorders (ROR_{025} = 11.51, IC_{025} = 3.45), coagulopathies and bleeding diatheses (ROR_{025} = 7.82, IC_{025} = 2.91) had the strongest signal values in AE associated with axicabtagene and tisagenlecleucel, respectively.

The differences between axicabtagene and tisagenlecleucel in hematologic adverse events

Therapy with axicabtagene and tisagenlecleucel resulted in 21 concurrent hematologic AE (Table 2). However, hematotoxicity and hemolytic anemia were only associated with axicabtagene (AE with <3 AE were not analyzed). In addition, only 15 hematologic AE were correlated with tisagen-

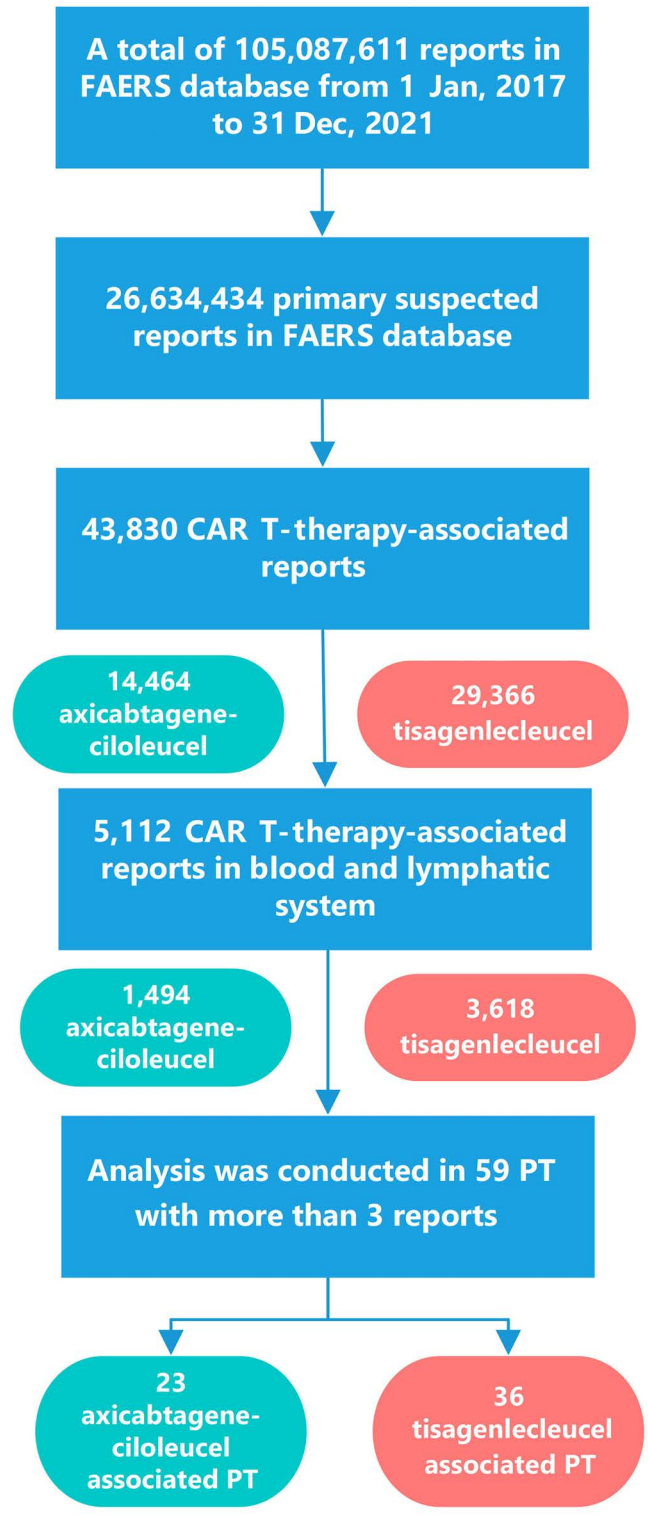


Figure 1. Study flowchart. From 1 January 2017 to 31 December 2021, a total of 105,087,611 adverse events were reported and 43,830 toxicity reports were associated with CAR T therapy. Among them, 5,112 reports were hematologic adverse events, and this study was performed among 38 preferred terms (PT) with more than 3 reports, of which 23 PT were related to axicabtagene and 36 related to tisagenlecleucel. CAR T: chimeric antigen receptor T cell.

lecleucel. The concurrent hematologic AE of these two CAR T products were further investigated to determine the differences between the treatment with axicabtagene and tisagenlecleucel. The reported frequency of tisagenlecleucel was significantly higher than axicabtagene for cytopenia (ROR=2.35, 95% CI: 1.87-2.96), coagulopathy (ROR=3.97, 95% CI: 2.28-6.92), and B-cell aplasia (ROR=2.51, 95% CI: 1.47-4.28) (Figure 2A). In contrast, the notably lower reported AE were neutropenia, febrile neutropenia, pancytopenia, HLH, bone marrow failure, hyperbilirubinemia, and neutropenic sepsis (ROR < 1) after tisagenlecleucel therapy.

When comparing the hematologic AE of these two CAR T products based on HLT, we found that tisagenlecleucel had a higher reported frequency in coagulopathies and bleeding diatheses (ROR=2.20, 95% CI: 1.62-2.98) and spleen disorders (ROR=6.47, 95% CI: 1.54-27.13), but lower in bone marrow depression (ROR=0.83, 95% CI: 0.76-0.90), hematologic disorders (ROR=0.61, 95% CI: 0.45-0.84), and hemolyses (ROR=0.53, 95% CI: 0.32-0.90) compared to axicabtagene (Figure 2B). Furthermore, there was a significant difference in time from CAR T infusion to the onset of hematologic AE between the axicabtagene and tisagenlecleucel groups (P<0.0001) (*Online Supplementary Figure 2A*). The time of onset of hematologic AE is faster and shorter for axicabtagene than for tisagenlecleucel. Similarly, significant differences were also observed among the top ten reported AE and six different HLT (*Online Supplementary Figure S2B and C*). Of note, most hematologic AE occurred within ten days following CAR T infusion.

Clinical characteristics of hematologic adverse events

To better understand the clinical characteristics of hematologic AE, we further explored the correlations between CRS, the most common toxicity after CAR T therapy, and the top ten most frequently reported hematologic AE (Figure 3A). Considerable overlap was observed between various hematologic AE and CRS, and most of the patients experienced more than one hematologic AE. The overlap between the hematotoxicity of the two CAR T products and CRS is shown in Figure 3B. Concurrent CRS and hematotoxicity were reported in 54.0% and 48.8% of axi-

Table 1. Baseline characteristics of patients with tisagenlecleucel- and axicabtagene-associated hematologic adverse events.

Variables	CAR T (N=5,112)	Axicabtagene (N=1,494)	Tisagenlecleucel (N=3,618)
Age in years, median (IQR)	31 (15-62)	59 (49-66)	20 (12-54)
Weight in kgs, median (IQR)	70.00 (52.00-82.30)	76.70 (67.00-87.00)	62.70 (38.00-82.00)
Gender, N (%)			
Female	1,879 (36.76)	476 (31.86)	1,403 (38.78)
Male	2,779 (54.36)	805 (53.88)	1,974 (54.56)
Missing events	454 (8.88)	213 (14.26)	241 (6.66)
Event year, N (%)			
2017	75 (1.47)	0 (0.00)	75 (2.07)
2018	465 (9.10)	189 (12.65)	276 (7.63)
2019	1,289 (25.22)	390 (26.10)	899 (24.85)
2020	1,944 (38.03)	475 (31.79)	1,469 (40.60)
2021	1,339 (26.19)	440 (29.45)	899 (24.85)
Outcome, N (%)			
Death	2,118 (41.43)	485 (32.46)	1,633 (45.14)
Disability	51 (1.00)	33 (2.21)	18 (0.50)
Hospitalization	819 (16.02)	391 (26.17)	428 (11.83)
Life-threatening	441 (8.63)	107 (7.16)	334 (9.23)
Other events	1,650 (32.28)	454 (30.39)	1,196 (33.06)
Missing events	33 (0.65)	24 (1.61)	9 (0.25)
Countries, N (%)			
United States	3,606 (70.54)	825 (55.22)	2,781 (76.87)
France	273 (5.34)	169 (11.31)	104 (2.87)
Germany	190 (3.72)	122 (8.17)	68 (1.88)
Spain	134 (2.62)	94 (6.29)	40 (1.11)
Italy	60 (1.17)	51 (3.41)	9 (0.25)
Netherlands	70 (1.37)	49 (3.28)	21 (0.58)
Great Britain	114 (2.23)	48 (3.21)	66 (1.82)
Portugal	35 (0.68)	35 (2.34)	0 (0.00)
Other countries	612 (11.97)	98 (6.56)	514 (14.21)
Missing events	18 (0.35)	3 (0.20)	15 (0.41)

CAR T: chimeric antigen receptor T cell; IQR: interquartile range; kgs: kilograms.

cabtagene and tisagenlecleucel recipients, respectively. Importantly, the rate of hematologic AE independent of CRS was approximately 49.5% (Figure 3B). The relationship between the six different HLT and CRS was further investigated, and correlation analyzes revealed that all hematologic AE were positively related to CRS (Figure 3C). Moreover, bone marrow depression, coagulopathies and bleeding diatheses, and hematologic disorders were strongly associated with CRS, while a weaker relationship was observed in spleen disorders and hemolyses.

To help clinicians detect highly lethal hematologic AE, we further calculated the fatality rates of different AE (number of death reports/AE reports) after CAR T therapy (Figure 4A and *Online Supplementary Table S5*). The results showed that 14 AE had a mortality rate of over 50% in tisagenlecleucel recipients, and only two AE after axi-

Table 2. Signal detection of tisagenlecleucel- and axicabtagene- associated hematologic adverse events.

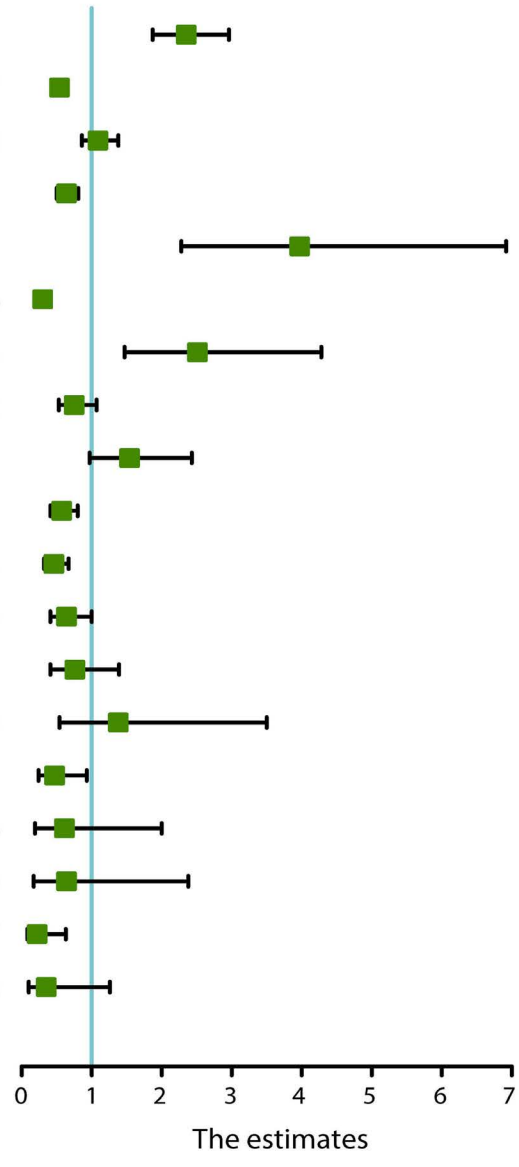
Preferred terms	CAR T			Axicabtagene			Tisagenlecleucel		
	a	ROR_{025}	IC_{025}	a	ROR_{025}	IC_{025}	a	ROR_{025}	IC_{025}
Cytopenia	517	56.38	5.65	90	21.97	4.38	427	66.05	5.90
Neutropenia	463	4.70	2.19	221	6.47	2.64	242	3.52	1.77
Thrombocytopenia	318	3.83	1.90	99	3.27	1.65	219	3.84	1.89
Febrile neutropenia	273	5.37	2.38	119	6.52	2.65	154	4.31	2.06
Pancytopenia	225	5.79	2.48	139	10.18	3.29	86	3.01	1.53
HLH	136	21.06	4.30	63	22.77	4.42	73	14.97	3.82
Anemia	129	0.83	-0.31	51	0.90	-0.23	78	0.71	-0.54
Coagulopathy	128	10.43	3.31	14	2.25	1.00	114	13.40	3.67
Bone narrow failure	112	4.88	2.23	58	6.77	2.68	54	3.19	1.60
DIC	99	9.64	3.19	24	5.18	2.25	75	10.26	3.28
B-cell aplasia	98	118.16	6.79	16	17.46	4.00	82	104.20	6.65
Lymphopenia	78	5.21	2.31	34	5.68	2.41	44	3.99	1.91
Leukopenia	43	0.87	-0.28	17	0.86	-0.35	26	0.72	-0.58
Hypofibrinogenemia	23	10.80	3.29	6	3.56	1.50	17	9.54	3.10
Hyperbilirubinemia	33	3.36	1.65	17	4.06	1.88	16	2.05	0.89
Splenomegaly	17	1.07	-0.04	2			15	1.34	0.27
Neutropenic sepsis	17	1.95	0.82	12	3.26	1.52	5	0.58	-1.16
Bone marrow disorder	13	3.24	1.51	1			12	3.97	1.80
Thrombotic microangiopathy	13	1.11	-0.03	7	1.34	0.13	6	0.59	-1.08
Purpura	12	1.26	0.15				12	1.81	0.67
Febrile bone marrow aplasia	11	1.66	0.53	5	1.43	0.13	6	1.07	-0.23
Agranulocytosis	10	0.50	-1.21	6	0.72	-0.81	4	0.22	-2.68
Hemolysis	9	0.87	-0.43	4	0.77	-0.87	5	0.58	-1.18
Hepatosplenomegaly	8	2.19	0.87				8	2.90	1.28
Aplastic anemia	7	1.02	-0.25	3	0.76	-1.06	4	0.67	-1.06
Hemolytic anemia	7	0.61	-1.00	5	1.01	-0.38	2		
Hematotoxicity	6	0.45	-1.47	5	0.93	-0.50	1		
Neutropenic colitis	4	0.90	-0.64				4	1.19	-0.24
Neutrophilia	4	0.31	-2.18				4	0.44	-1.67
Normocytic anemia	4	0.83	-0.76				4	1.10	-0.35
White blood cell disorder	4	0.67	-1.06				4	0.92	-0.61
Autoimmune hemolytic anemia	4	0.48	-1.56	1			3	0.44	-1.83
B-lymphocyte abnormalities	3	1.91	0.32				3	1.99	0.38
Jaundice	3	0.07	-4.42				3	0.11	-3.86
Normochromic normocytic anemia	3	0.66	-1.25				3	0.87	-0.86
Petechiae	3	0.15	-3.41				3	0.21	-2.88
Splenic hemorrhage	3	1.23	-0.36				3	1.44	-0.12
Splenic infarction	3	0.70	-1.17				3	0.91	-0.80

HLH: hemophagocytic lymphohistiocytosis; DIC: disseminated intravascular coagulation; CAR T: chimeric antigen receptor T cell; ROR: reporting odds ratio; IC: information component. Blank means not applicable.

cabtagene therapy. However, eight AE had fewer than ten death reports among the over 14 AE reported after tisagenlecleucel therapy (*Online Supplementary Table S5*). Importantly, the fatality rates of the five highly underestimated hematologic AE, HLH, coagulopathy, bone marrow failure, DIC and B-cell aplasia were 69.9%, 47.7%, 27.7%, 59.6%, and 17.1%, respectively (Figure 5). Notably, death rates were higher after axicabtagene than after tisagenlecleucel in HLH (74.60% *vs*. 65.75%), DIC (66.67% *vs*. 57.33%), and coagulopathy (50% *vs*. 47.37%). Nevertheless, axicabtagene had a lower death rate than tisagenlecleucel in patients with bone marrow failure (25.9% *vs*. 29.6%). An analysis in terms of HLT showed a higher proportion of death in spleen disorders, hemolyses, coagulopathies and bleeding diatheses, and bone marrow depression after tisagenlecleucel therapy compared to axicabtagene (Figure 4B and *Online Supplementary Table S6*). However, the death rate of hematologic disorders was reported to be lower in patients treated with tisagenlecleucel than in those treated with axicabtagene. Finally, LASSO regression analysis was performed to identify

A

PT	a	b	c	d	IC025	ROR (95% CI)
Cytopenia	90	14374	427	28939	0.14	2.35(1.87,2.96)
Neutropenia	221	14243	242	29124	−0.57	0.54(0.45,0.64)
Thrombocytopenia	99	14365	219	29147	−0.18	1.09(0.86,1.38)
Febrile neutropenia	119	14345	154	29212	−0.51	0.64(0.50,0.81)
Coagulopathy	14	14450	114	29252	0.10	3.97(2.28,6.92)
Pancytopenia	139	14325	86	29280	−1.16	0.30(0.23,0.40)
B-cell aplasia	16	14448	82	29284	−0.05	2.51(1.47,4.28)
Anemia	51	14413	78	29288	−0.52	0.75(0.53,1.07)
Disseminated intravascular coagulation	24	14440	75	29291	−0.21	1.54(0.97,2.43)
Hemophagocytic lymphohistiocytosis	63	14401	73	29293	−0.71	0.57(0.41,0.80)
Bone marrow failure	58	14406	54	29312	−0.93	0.46(0.32,0.67)
Lymphopenia	34	14430	44	29322	−0.75	0.64(0.41,1.00)
Leukopenia	17	14447	26	29340	−0.81	0.76(0.41,1.39)
Hypofibrinogenemia	6	14458	17	29349	−0.69	1.38(0.54,3.50)
Hyperbilirubinemia	17	14447	16	29350	−1.31	0.47(0.24,0.93)
Febrile bone marrow aplasia	5	14459	6	29360	−1.76	0.61(0.19,2.00)
Hemolysis	4	14460	5	29361	−1.90	0.64(0.17,2.38)
Neutropenic sepsis	12	14452	5	29361	−2.77	0.22(0.08,0.63)
Agranulocytosis	6	14458	4	29362	−2.58	0.35(0.10,1.26)



B

HLT	a	b	c	d	IC025	ROR (95% CI)
Bone marrow depression	1481	27885	870	13594	−0.17	0.83(0.76,0.90)
Coagulopathies and bleeding diatheses	227	29139	51	14413	0.07	2.20(1.62,2.98)
Spleen disorders	29	29337	2	14462	−0.15	6.47(1.54,27.13)
Hematologic disorders	86	29280	69	14395	−0.63	0.61(0.45,0.84)
Hemolyses	29	29337	27	14437	−0.99	0.53(0.32,0.90)
Other events	1766	27600	475	13989	0.16	1.88(1.70,2.09)

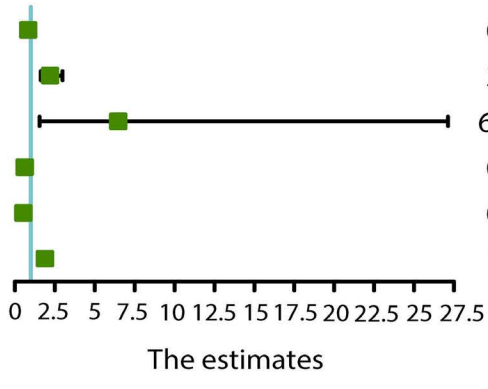


Figure 2. Signal comparison between tisagenlecleucel and axicabtagene (tisagenlecleucel *vs*. axicabtagene) in different adverse events. (A) Signal comparison between tisagenlecleucel and axicabtagene (tisagenlecleucel *vs*. axicabtagene) in different preferred terms (PT). (B) Signal comparison between tisagenlecleucel and axicabtagene (tisagenlecleucel *vs*. axicabtagene) in different high level terms (HLT). DIC: disseminated intravascular coagulation; HLH: hemophagocytic lymphohistiocytosis.

hematologic AE that were strongly associated with death (*Online Supplementary Figure S3*). Twenty-two hematologic AE were identified to be closely related to death in CAR T recipients, including cytopenia, DIC, febrile neutropenia, HLH, splenic hemorrhage, and thrombocytopenia (Table 3).

Discussion

CAR T therapy has revolutionized the treatment of patients with r/r hematologic malignancies due to its high clinical efficacy compared to traditional chemotherapy. There has

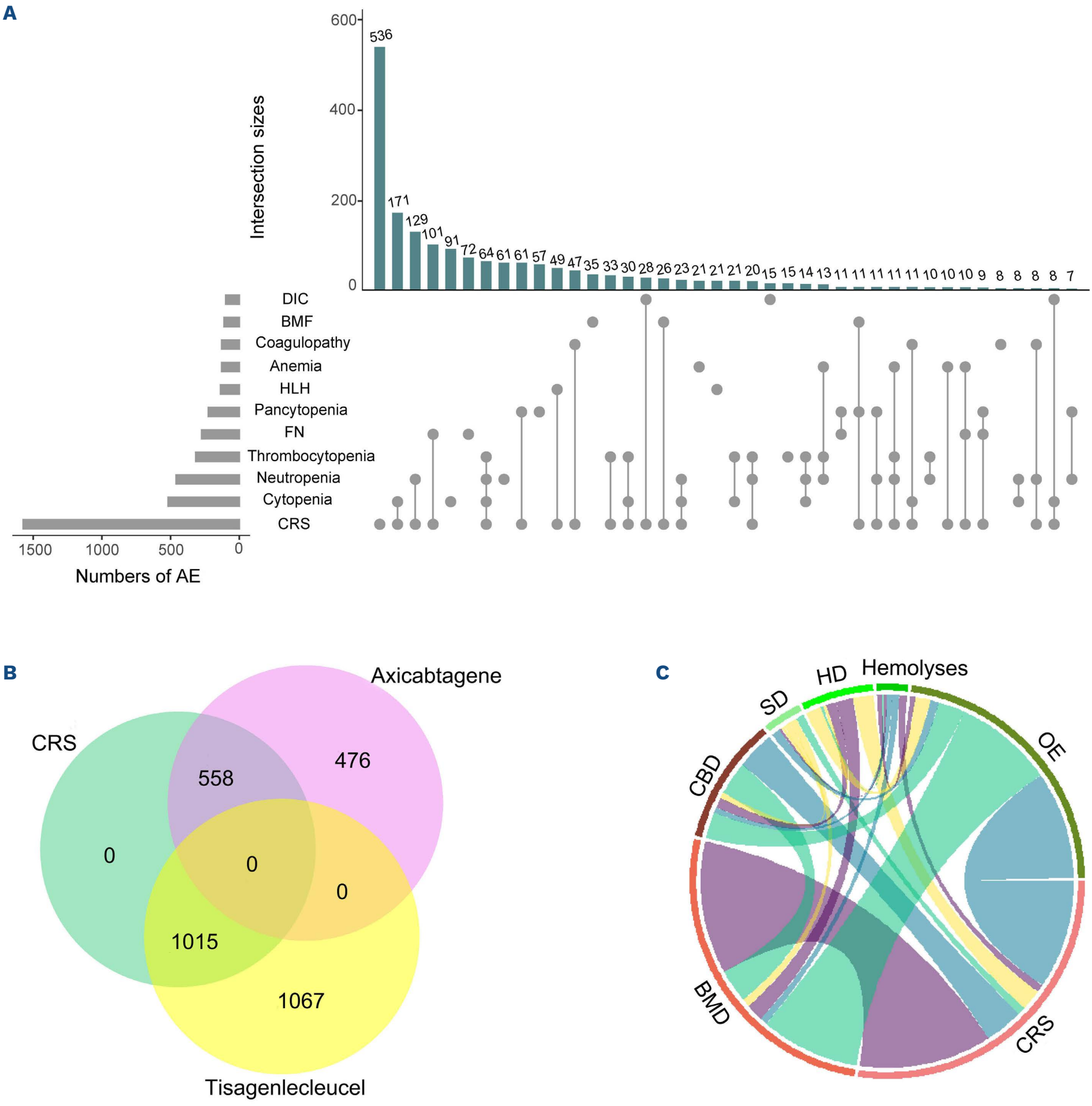


Figure 3. Correlation between cytokine release syndrome and various hematologic adverse events. (A) Overlap between cytokine release syndrome (CRS) and top 10 CAR T-associated hematologic adverse events. (B) Overlap between CRS, axicabtagene- and tisagenlecle-associated hematologic adverse events. (C) Overlap between CRS and 6 high level terms (HLT) of hematologic adverse events. CAR T: chimeric antigen receptor T cell; DIC: disseminated intravascular coagulation; HLH: hemophagocytic lymphohistiocytosis; BMD: bone marrow depression; CBD: coagulopathies and bleeding diatheses; SD: spleen disorders; HD: hematologic disorders; OE: other events.

been a consistent increase in the use of CAR T therapy in recent years, and the number of CAR T therapies had increased by 24% in 2022 compared to 2021.[19] With more and more people are now eligible for CAR T therapy, it is essential to comprehensively determine treatment-related AE and differences among various CAR T products to optimize this revolutionary therapy. Hematotoxicity is the most common long-term toxicity in CAR T recipients, with severe outcomes. However, clinical trials have never been sufficiently powered to detect hematologic AE because the patients enrolled in the study had been highly selected.

In this study, we extensively investigated CAR T-associated hematotoxicity using FAERS, which is instrumental in the early detection and prevention of some rare but fatal AE. To the best of our knowledge, this is the largest post-marketing study of CAR T-associated hematologic AE. Of the 43,830 CAR T-associated AE reported, 5,112 (11.7%) were hematologic AE. The analysis revealed that younger patients (age <65 years) were more likely to experience hematologic AE (age <65 *vs*. ≥65 years, ROR_{025} = 1.23) (*Online Supplementary Table S2*), according to a meta-analysis of hematologic toxicity in CAR T recipients.[20] This may be associated with a more potent immune response after CAR T infusion in younger patients. In general, the incidence of hematologic toxicity was significantly higher after infusion with tisagenlecleucel than axicabtagene (*Online Supplementary Table S2*). Tisagenlecleucel was approved for the treatment of patients with r/r DLBCL and r/r B-ALL, and axicabtagene only for r/r DLBCL. Therefore, the rate of cytopenia-related hematotoxicity could be higher with tisagenlecleucel than with axicabtagene. In addition, this finding may also be associated with the different co-stimulatory domains of these two CAR T products, CD28 and 4-1BB for axicabtagene and tisagenlecleucel, respectively.[4] Co-stimulation of 4-1BB mediates longer persistence of CAR T cells than CD28[21] and it is reasonable to observe more reports of hematologic AE in tisagenlecleucel, especially long-term and delayed hematologic AE, such as B-cell aplasia.

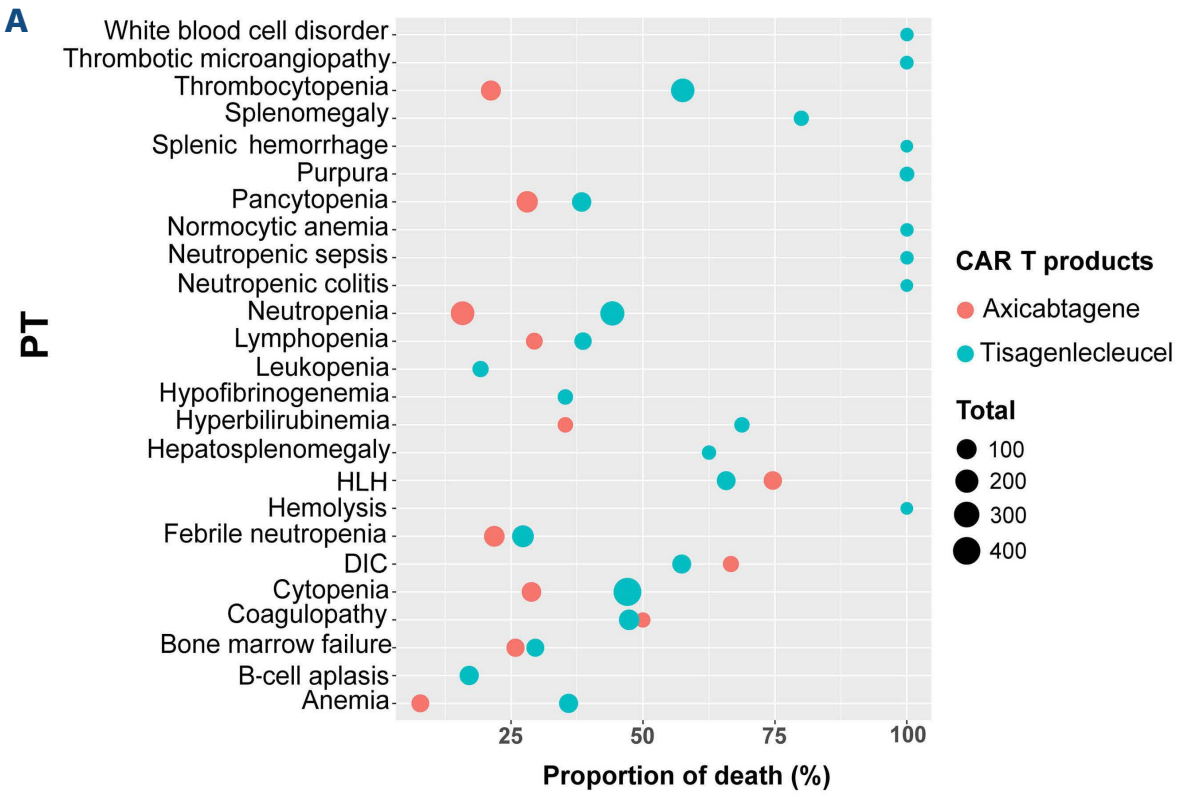
Our analysis identified the possible top ten significant hematologic AE after CAR T therapy: cytopenia, neutropenia, thrombocytopenia, febrile neutropenia, pancytopenia, HLH, coagulopathy, bone marrow failure, DIC and B-cell aplasia. (Table 2). According to pivotal clinical trials,[4,14,22-24] a high number of reports of cytopenia, neutropenia, thrombocytopenia, febrile neutropenia, and pancytopenia were also observed. However, there are few reports of HLH, coagulopathy, bone marrow failure, DIC, and B-cell aplasia, suggesting that these over-reported hematologic AE were largely underestimated in clinical trials. The reason may be associated with strict inclusion criteria and the careful selection of patients in these clinical trials.[4,14] Moreover, HLH and DIC had substantial fatality rates of 69.9% and 59.6%, respectively. In particular, the incidence of HLH was significantly lower in patients receiving tisagenlecleucel than in those receiving axicabtagene, and the death rates of HLH and DIC were higher after infusion of axicabtagene than tisagenlecleucel (Figures 2A, 4A). According to the reported studies by ZUMA-1 and JULIET,[4,24] one patient died from HLH out of 119 patients receiving axicabtagene, while there were no deaths related to HLH out of 167 patients receiving tisagenlecleucel. HLH and DIC are rapidly progressing life-threatening hematologic AE that need to be monitored, and clinicians must stay on the alert for these rare but fatal hematologic AE in CAR T recipients, especially those receiving axicabtagene. Furthermore, we identified a strong correlation between HLH, DIC, and CRS (Figure 3C), in accordance with previously published studies.[25-27] Therefore, tisagenlecleucel could reduce the risk of HLH and DIC in patients who are more likely to develop serious CRS, such as a high tumor burden prior to the infusion of CAR T.[28]

Table 3. Death-associated hematologic adverse events selected from K-fold cross-validation LASSO regression.

Preferred terms	S3	S6
Agranulocytosis	-0.63	-0.75
Anemia	-0.19	-0.22
Aplastic anemia	-0.52	-0.64
Autoimmune hemolytic anemia	-0.07	-0.21
B-cell aplasia	-0.75	-0.79
Bone marrow disorder	-0.28	-0.36
Bone marrow failure	-0.09	-0.12
Cytopenia	0.14	0.14
DIC	0.59	0.61
Febrile neutropenia	-0.44	-0.46
HLH	1.16	1.19
Leukopenia	-1.19	-1.31
Neutropenia	-0.28	-0.31
Neutropenic colitis	0.03	0.17
Normocytic anemia	2.18	2.42
Pancytopenia	-0.01	-0.03
Post depletion B-cell recovery	-1.06	-1.15
Purpura	1.33	1.40
Splenic hemorrhage	0.92	1.06
Splenomegaly	0.78	0.85
Thrombocytopenia	0.39	0.42
White blood cell disorder	0.99	1.11

DIC: disseminated intravascular coagulation; HLH: hemophagocytic lymphohistiocytosis. S3 and S6 are co-efficients of PT selected from 3-fold and 6-fold cross-validation LASSO regression, respectively.

In addition to HLH and DIC, coagulopathy is also an underestimated but severe hematologic toxicity related to CAR T in clinical trials, always causing bleeding and thrombosis in CAR T recipients.[29] Our findings suggest the fatality rate of coagulopathy is 47.7% (Figure 5). Tisagenlecleucel has been reported to have a higher rate of coagulopathy than axicabtagene (Table 2 and Figure 2A), which is consistent with published research in which 56.6% and 15.7% of patients suffered from coagulopathy after tisagenlecleucel and axicabtagene, respectively.[29,30] B-cell aplasia, an 'off-target' event, was also reported to be more common in patients receiving tisagenlecleucel than in those receiving axicabtagene (Figure 2A). This may be due to longer-lasting co-stimulation of tisagenlecleucel, leading to longer persistence of CAR T, which are more likely to cause off-target AE. On the contrary, the frequency of bone marrow failure after infusion of tisagenlecleucel was lower than after axicabtagene. These findings revealed that we could optimize the choice of CAR T products prior to the therapy according to each patient's basic profile, thus reducing the risk of severe toxicities. Furthermore, early detection of these under-reported but lethal hematologic AE is essential because the patients we treated were not always subjected to strict selection criteria, unlike those on clinical trials.
Neutropenia was the most frequently reported hematologic AE for axicabtagene (Table 2), which is consistent



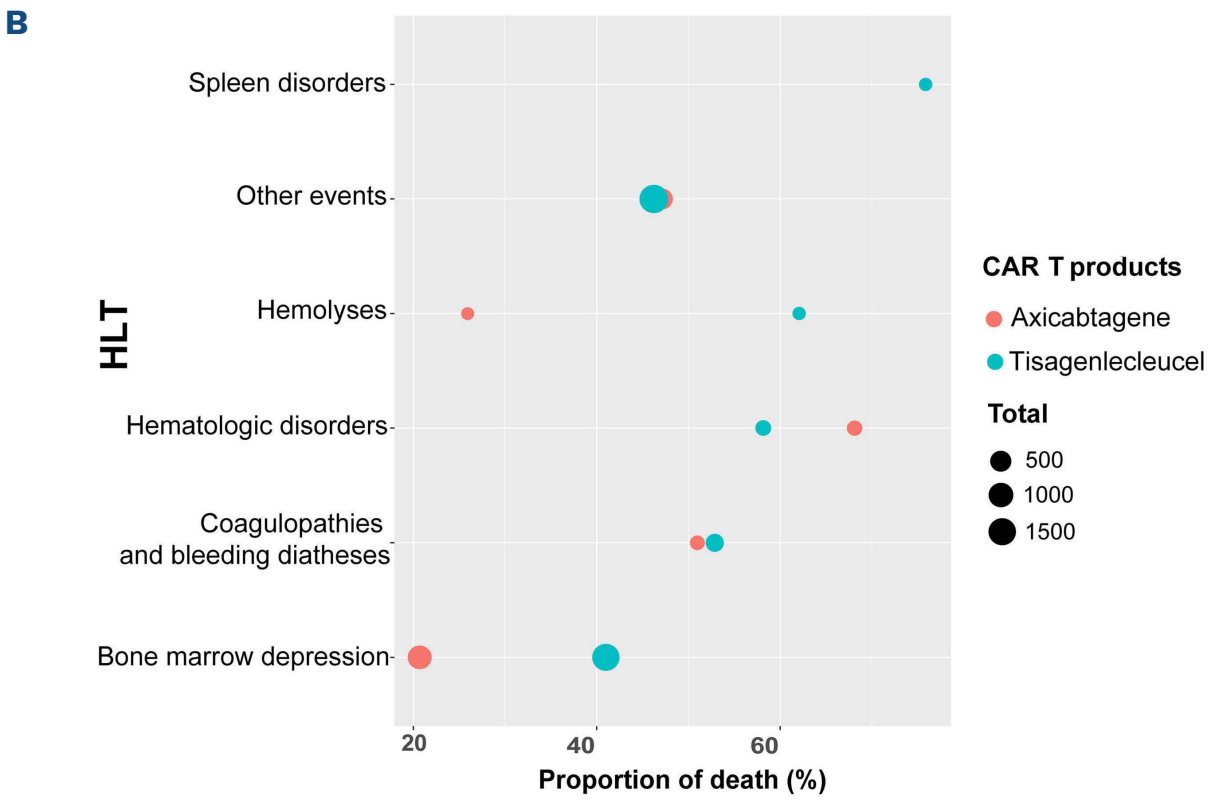


Figure 4. Mortality rates of various hematologic adverse events following axicabtagene and tisagenlecleucel therapy. (A) Proportion of death in different preferred terms (PT) of hematologic adverse events. (B) Proportion of death in different high level terms (HLT) of hematologic adverse events. DIC: disseminated intravascular coagulation; HLH: hemophagocytic lymphohistiocytosis.

with previous clinical trials.[23,31] In a multicenter phase II clinical trial of patients with refractory large B-cell lymphoma treated with axicabtagene, neutropenia was also the most common serious AE (grade ≥ 3).[23] In particular, neutropenia can predispose patients to infection, which is the most common cause of NRM.[2,32] Therefore, neutropenia must be prevented in patients receiving axicabtagene therapy by, for example, ensuring sufficient blood preparation prior to CAR T infusion and correct administration of hematopoietic growth factors after CAR T infusion. In addition, baseline cytopenia and high levels of C-reactive protein and ferritin prior to the therapy have been reported to be closely related to neutropenia after CAR T infusion.[9] Therefore, correcting baseline cytopenia and reducing pretreatment levels of inflammatory factors can reduce the risk of neutropenia in CAR T recipients. In addition, early or prophylactic stimulation of hematopoietic stem cells may improve the outcomes of persistent neutropenia after CAR T infusion.[33] For patients receiving tisagenlecleucel therapy, the highest reported frequency of hematologic AE was cytopenia, which is consistent with a phase II clinical trial.[14]

Febrile neutropenia was reported to have a significantly lower frequency in tisagenlecleucel recipients compared to axicabtagene, corresponding to ROR=0.64 (95% CI: 0.50-0.81) (Figure 2A). This finding is in line with the pivotal data reported from the JULIET and ZUMA-1 studies with 17% and 36% febrile neutropenia,[4,24] respectively. Similarly, a lower reported frequency was observed in pancytopenia and hyperbilirubinemia after tisagenlecleucel therapy. Importantly, pancytopenia is a hallmark of hyperactive immune diseases, such as HLH,[25] which also had a lower reported frequency in tisagenlecleucel than in axicabtagene. This finding further confirmed that tisagenlecleucel may be more suitable for patients at high risk for HLH, such as those with a genetic profile associated with HLH.[34] The time of onset of hematologic AE was shorter after axicabtagene infusion than after tisagenlecleucel infusion (*Online Supplementary Figure S2*). This may be due to the faster expansion of CAR T for axicabtagene than for tisagenlecleucel.[35] Most patients suffered from hematologic AE within ten days after CAR T infusion, and a small proportion of patients experienced delayed hematotoxicity at 30 days or longer, which is consistent with previous studies.[4,36] CRS is the most common AE, according to published data and real-world studies.[2,14,37] The overlap between CRS, the top ten reported hematologic AE and two CAR T products was further analyzed to explore their relationship (Figure 3). Most patients had concurrent hematologic AE and CRS, which may be due to the detrimental effects of high concentrations of various cytokines on stem cells. For example, high levels of interleukin-6 and tumor necrosis factor alpha have been reported to damage the bone marrow microenvironment,[38,39] and interferon-γ can impair hematopoietic stem cell proliferation.[40] Therefore, early administration of tocilizumab to treat CRS may reduce the risk of hematologic AE. The frequency of concurrent CRS and hematotoxicity was higher in patients receiving axicabtagene than in those receiving tisagenlecleucel (54.0% *vs.* 48.8%). This may be associated with quicker expansion of CAR T and stronger hyperactive immune response in axicabtagene therapy, given their different co-stimulatory domains.[35] It should be noted that 49.5% of patients reported hematotoxicity independently of CRS, suggesting that other off-target AE were associated with hematotoxicity in CAR T therapy.

Various hematologic AE were further divided into six subgroups based on HLT: bone marrow depression, coagulopathies and bleeding diatheses, hematologic disorders, hemolyses, spleen disorders, and other events (*Online*

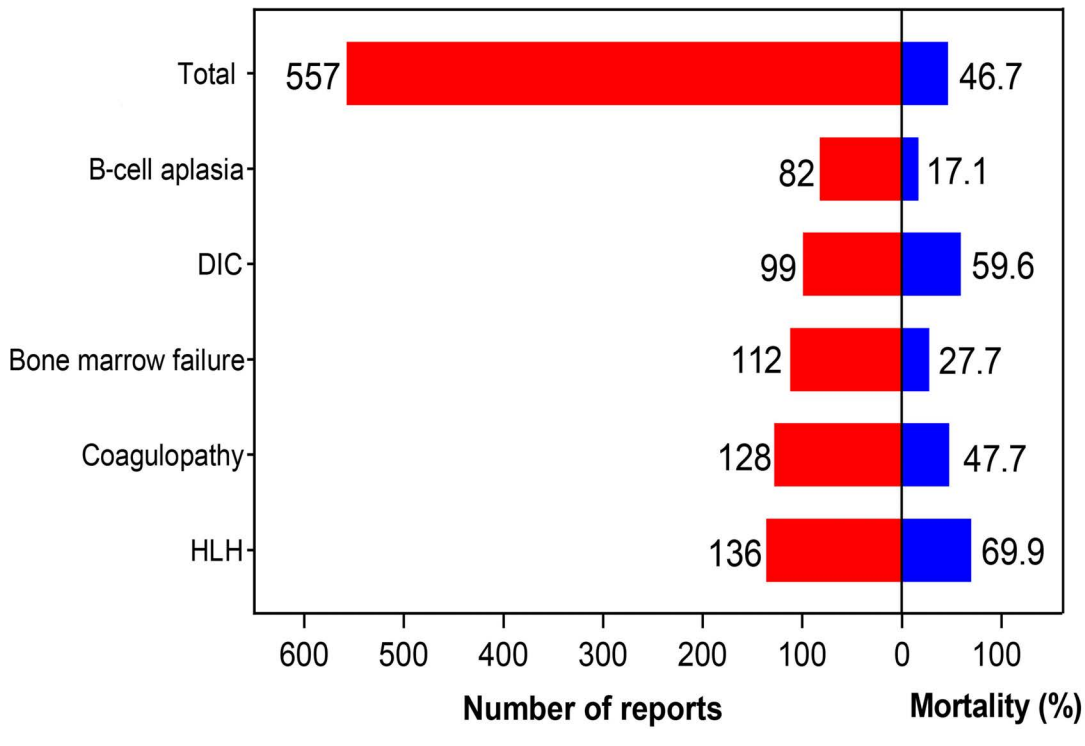


Figure 5. Number of reports and mortality rates of 5 highly underestimated hematologic adverse events in clinical trials. These include B-cell aplasia, disseminated intravascular coagulation (DIC), bone marrow failure, coagulopathy, and hemophagocytic lymphohistiocytosis (HLH).

Supplementary Table S3). The results suggested that bone marrow depression, coagulopathies and bleeding diatheses, and hematologic disorders were strongly correlated with CRS (Figure 3C). According to previous findings, CRS manifestations include cytopenia, fever, coagulopathy, HLH, DIC, and end-organ dysfunction.[41,42] Furthermore, hypofibrinogenemia coagulopathy has been reported to correlate with severe CRS in tisagenlecleucel therapy.[43,44] In contrast, a weak correlation was observed between CRS and hemolyses and spleen disorders. In particular, the strongest connection was observed between bone marrow depression and CRS, and the probable reason could be that CRS was the risk factor for bone marrow depression.[10,36]

In terms of death reports, the mortality rates of HLH, DIC and coagulopathy were higher in patients treated with axicabtagene than in those treated with tisagenlecleucel (Figure 4A). Although the pathophysiology of HLH and DIC associated with CAR T remains unclear, numerous studies have postulated that severe CRS plays a vital role in triggering the occurrence of HLH and DIC.[41,45] Previous clinical trials have found that the rates of severe CRS (grade ≥3) after treatment with axicabtagene and tisagenlecleucel were 7-9% and 1-5%, respectively.[2,21,46] This may be the reason why higher frequency and mortality rates of HLH and DIC were observed after axicabtagene compared to tisagenlecleucel. Coagulopathy is strongly correlated with CRS.[47] Therefore, vigilant monitoring of HLH, DIC, and coagulopathy is needed in patients with severe CRS. Moreover, there was a 100% death rate for hemolysis, neutropenic colitis, neutropenic sepsis, normocytic anemia, purpura, splenic hemorrhage, thrombotic microangiopathy, and white blood cell disorder after infusion of tisagenlecleucel (Figure 4A and *Online Supplementary Table S5*). However, there are few reports of these hematologic AE and further research is warranted.

In the LASSO regression analysis, 22 hematologic AE were associated with death in patients receiving CAR T therapy, such as cytopenia, HLH, and DIC (Table 3). In particular, all of the top ten reported hematologic AE were related to death, except coagulopathy. Combined with the results of the analysis of the fatality rate (Figure 4A), we found that HLH and DIC were life-threatening hematologic AE, with death rates exceeding 50% in both axicabtagene and tisagenlecleucel.

In summary, this post-marketing report analysis comprehensively revealed CAR T-related hematologic AE and compared the differences between axicabtagene and tisagenlecleucel. In general, HLH and DIC were largely under-reported, but fatal hematologic AE in CAR T recipients. These findings were instrumental in optimizing the choice of CAR T products according to the pre-treatment patient profile and in preventing rarely reported hematologic AE, reducing the risk of lethal toxicities, and improving the prognosis of CAR T recipients.

This study has some limitations. FAERS is the largest global repository of post-marketing drug AE reports, encompassing more than 28 million AE reports. It plays a vital role in post-marketing surveillance to characterize drug-associated AE, and provides a reliable foundation for developing ideas, generating hypotheses, and constructing study designs. However, the number of patients treated with axicabtagene and tisagenlecleucel has not been reported in FAERS. Therefore, the incidence of CAR T-associated hematologic AE remains unknown.

FAERS is a voluntary reporting system with the limitation that data on patients, disease, treatment, and outcomes are fragmented and unsystematic. Consequently, information was missing for some variables, such as age and sex. Meanwhile, there are some overlapping toxicities between cytopenia and anemia, thrombocytopenia, and neutropenia. Importantly, the treatment responses and prognosis of patients following CAR T therapy is unclear. In contrast to clinical trials, the comparison between axicabtagene and tisagenlecleucel is limited by the potential unbalanced characteristics of the patient population. However, clinical trials could not fully reflect AE due to restrictive inclusion criteria and careful patient selection, leading to some rare hematologic AE being underestimated. Therefore, a real-world study is essential to comprehensively identify hematologic AE related to CAR T cells, especially in identifying rare but life-threatening AE.

Disclosures

No conflicts of interest to disclose.

Contributions

YW, JY and ZT are responsible for study concept, methodology and software. ZS, DT and GT are responsible for data curation, and prepared and wrote the original draft. ZS, DT and GT are responsible for visualization and investigation of data. YW supervised the study. ZS, DT and NL are responsible for software and data validation. YW, JY and ZT wrote, reviewed and edited the paper.

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Data-sharing statement

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).

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