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Adverse drug event signal detection and risk factor analysis of blinatumomab in ten years of post-marketing use

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ABSTRACT

Objective: To analyze factors influencing the safety of blinatumomab based on real-world adverse drug event (ADE) reports collected from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) over the last decade since its market approval, thereby strengthening pharmacovigilance for high-risk populations.

Methods: Data from the FAERS database from the fourth quarter of 2014 to the third quarter of 2024 were retrieved. ADE positive signals were systematically classified, and six types of adverse events with high incidence, strong specificity, and high correlation were analyzed, including neurological disorders, cytokine release syndrome (CRS), immune system disorders, hematologic and lymphatic system disorders, infections and infestations, and lineage switch. For each type, statistical analyses were performed according to potential influencing factors, including age, sex, body weight, interval time, and continent of patient origin.

Results: A total of 18,728 ADE reports associated with blinatumomab were collected, from which 371 positive signals were identified, involving 20 system organ classifications (SOCs). The preferred term (PT) with the strongest signal was lineage switch leukemia, an adverse event not mentioned in the prescribing information. The SOC with the highest frequency was neurological disorders. Except for lineage switch leukemia, significant differences in influencing factors were observed across the other five adverse event categories. Analysis of the overall population of ADE suggested that Asian juvenile and elderly patients showed lower drug tolerability, and juvenile patients were more prone to delayed adverse events.

Conclusion: In clinical use of blinatumomab, particular attention should be paid to drug tolerability in Asian populations, with vigilance for early-onset and delayed adverse events. Given the short duration of blinatumomab's availability in China and limited local experience, enhanced drug monitoring and risk prevention are warranted for juvenile and elderly patients in clinical practice.

Introduction

Blinatumomab is the first approved bispecific antibody, also known as a bispecific T-cell engager (BiTE) worldwide,[1] and has demonstrated significant efficacy in high-risk adult and pediatric patients with primary refractory or relapsed precursor B-cell acute lymphoblastic leukemia (BCP-ALL).[2–4] Blinatumomab was approved in the United States at the end of 2014 and entered the Chinese market in December 2020. It is currently approved in China for the treatment of adult and pediatric patients with relapsed or refractory CD19-positive BCP-ALL.[1,2] Although blinatumomab has shown remarkable efficacy in clinical trials, severe adverse events (AEs) such as cytokine release syndrome (CRS), neurotoxicity, and infections remain major concerns, as they may lead to treatment discontinuation and even pose life-threatening risks.[5,6] Therefore, drug-related adverse events require close monitoring. In this study, we collected and summarized blinatumomab-related AE reports from FAERS database, identified potential previously unreported AEs, and conducted a categorical analysis of risk factors to explore the characteristics, patterns, and influencing factors of AE occurrence. Based on these findings, we propose corresponding preventive measures to provide a guidance for the long-term clinical management of blinatumomab.

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Materials and methods

Data sources and screening

As shown in Fig. 1, based on the blinatumomab's market approval date, all report files from the American Standard Code for Information Interchange (ASCII) data packages of FAERS database were downloaded for the period from the fourth quarter of 2014 to the third quarter of 2024 and imported into SAS 9.4 software. Data cleaning was performed following the FDA's recommended deduplication method.[7] Specifically, the PRIMARYID, CASEID, and FDA_DT fields in the DEMO table were used. The records were sorted by CASEID, FDA_DT, and PRIMARYID. For reports with the same CASEID, only the record with the latest FDA_DT was retained. If both CASEID and FDA_DT were identical, the record with the largest PRIMARYID was retained. The target population was identified using the "PROD_AI" by selecting records containing "blinatumomab" and restricting the role code to "Primary Suspect" (PS). When defining the target drug user group, only patients for whom the drug of primary suspicion was the study drug were included. If the primary suspected drug in the background database was the study drug, the patient was included in the target drug group. Otherwise, the patient was assigned to the non-target drug group. Reports unrelated to the drug, such as those involving tumor metastasis, disease progression, product issues, or procedural events such as intubation, were removed to reduce bias. Extracted variables included sex, age, body weight, country, continent of reporting country, reporting year, and the time interval between the onset date of the adverse event and the drug initiation date.

Data processing

In this study, ADE signals were coded, classified, and described using the preferred terms and SOCs from the Medical Dictionary for Regulatory Activities (MedDRA), version 27.0.

Signal identification and statistical analysis

At present, there is no universally accepted standard for selecting signal detection methods for adverse event analysis. Commonly used approaches include the Reporting Odds Ratio (ROR), the Proportional Reporting Ratio (PRR), and the Bayesian Confidence Propagation Neural Network (BCPNN) method.[8,9] The ROR and PRR methods are calculated based on disproportionality analysis using a fourfold contingency table (Table 1). These methods compare the reporting frequency of a target drug-event pair with its background frequency, offering high sensitivity and low bias. However, they have limited specificity and are prone to false positives, thus requiring validation with additional methods.[8] In contrast, the BCPNN method (Table 2) integrates Bayesian logic with a neural network framework, yielding more stable results, higher specificity, and effective reduction of false positives.[9] All the three methods were used in combination to detect

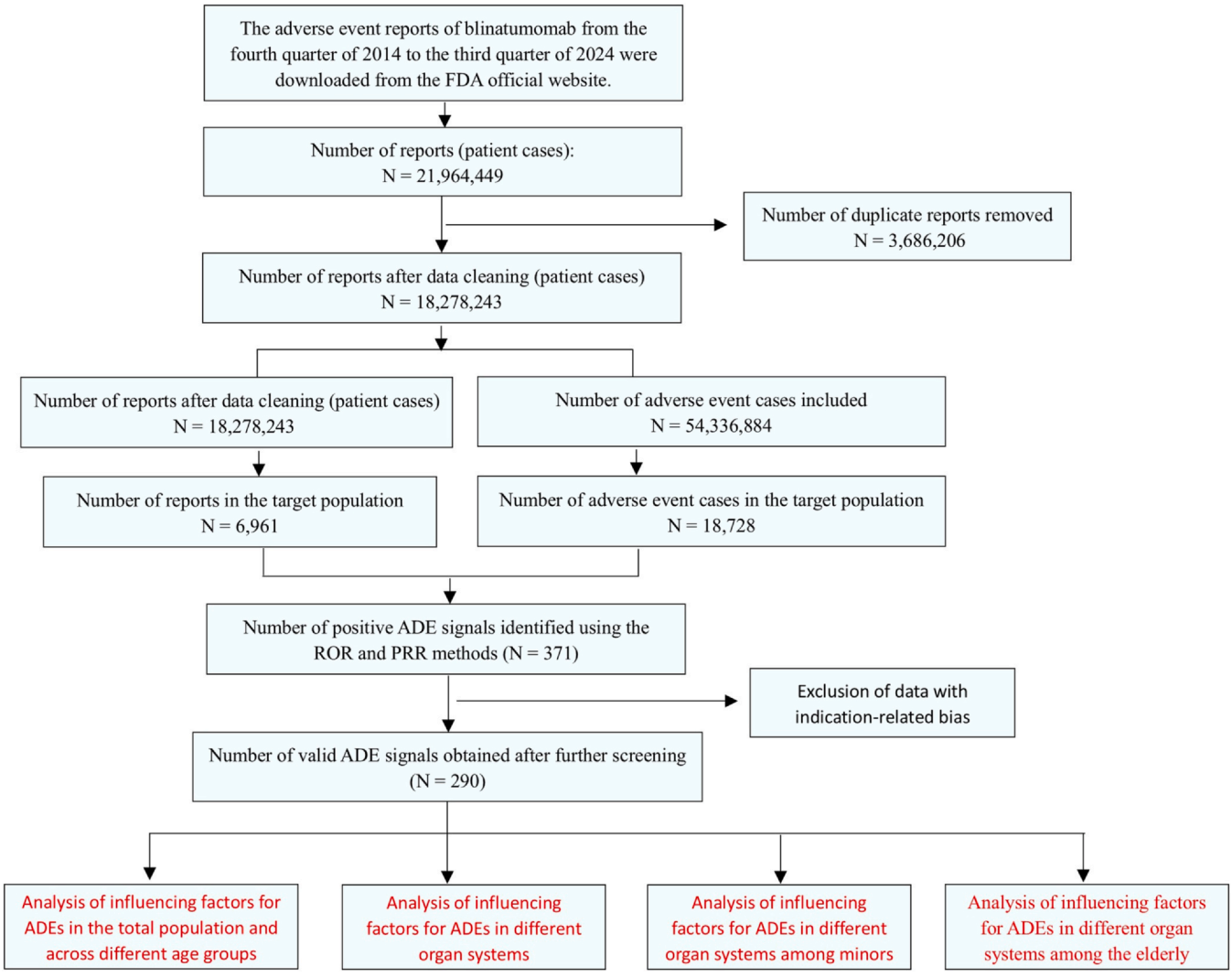

Fig. 1. Flowchart for screening adverse reaction signals of blinatumomab.

Table 1
Four-fold table of the proportional imbalance method.

	Target adverse event cases	Other adverse event cases	Total
Target drug	a	b	a + b
Other drugs	c	d	c + d
Total	a + c	b + d	N = a + b + c + d

Table 2
Bayesian confidence propagation neural network method.

Computational formula	Threshold
$IC = \log_2 \frac{p(x,y)}{p(x)p(y)} = \log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$ $E(IC) = \log_2 \frac{(a+y11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b)(a+c)}$ $V(IC) = \frac{1}{(in2)^2}\left\{\left[\frac{(a+b+c+d)-a+y-y11}{(a+y11)(1+a+b+c+d+y)}\right]+\left[\frac{(a+b+c+d)-(a+b)+a-a1}{(a+b+a1)(1+a+b+c+d+a)}\right]+\left[\frac{(a+b+c+d)-(a+b)c+\beta-\beta1}{(a+c+\beta1)(1+a+b+c+d+\beta)}\right]\right\}$ $\gamma = \gamma 11 \frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+a1)(a+b+\beta1)}$ $IC - 2SD = E(IC) - 2\sqrt{V(IC)}$ $\alpha 1 = \beta 1;\ \alpha = \beta = 2;\ \gamma 11 = 1$	If the lower limit of the confidence interval (IC-2SD) is greater than 0, one signal is generated.

risk signals for blinatumomab. The calculated metrics included ROR values with their 95 % confidence intervals (CIs), PRR values, χ^2 statistics, and Information Component (IC) values with their 95 % CIs. The criteria for identifying a positive signal were as follows: (1) ROR method: number of reports ≥ 3 and lower limit of the 95 % CI for ROR ≥ 1[8]; (2) PRR method: number of reports ≥ 3, PRR ≥ 2, and $\chi^2 \geq 4$[8]; (3) BCPNN method: lower limit of the IC's credibility interval (IC-2SD) > 0.[9] Only ADEs meeting the positive signal thresholds in all three methods were included in the final analysis. Larger ROR and PRR values indicate stronger signals and a higher likelihood of an association between the drug and the ADE.[10] Data processing was performed using SPSS (version 27.0) and Microsoft Excel 2021.

Results

Overview of ADE reports and demographic characteristics

A total of 18728 ADE reports listing blinatumomab as the primary suspected drug were retrieved from the FAERS database since October 1, 2014. As of November 2024, demographic information was updated through September 30, 2024, and 6961 ADE reports with available demographic data were collected. Among these reports, the proportion of male patients (38.79 %) was slightly higher than that of female patients (38.79 % vs 33.21 %). The majority of cases were reported in young adults aged 18–44 years (19.02 %) and middle-aged adults aged 45–64 years (15.01 %). Among 3883 patients with reported age, the mean age was 39.3 years, with a median (interquartile range) of 40 (19, 60) years. The youngest reported patient was 0.01 years old, and the oldest was 92 years old. The United States and North America accounted for the largest proportion of reports, representing 57.48 % of the total, and the number of reports showed an increasing trend over time. Detailed results are presented in Table 2.

PTs involved in ADE signals

In total, 371 positive ADE signals were identified. After excluding PTs related to the blinatumomab's indication, unrelated to drug administration, or influenced by the protopathy, 290 ADE signals remained, involving 20 SOCs and encompassing 8010 individual ADE reports. The top 30 PTs were ranked in descending order according to frequency (a value) and signal strength (ROR value), as shown in Table 3. After integration, the 10 most frequently reported ADEs were fever, cytokine release syndrome, neurotoxicity, tremor, neutropenia, confusional state, seizure, infection, febrile neutropenia, and hypotension. The 10 ADEs with the strongest signal strength (highest ROR values) were leukemia lineage switch, CD19 antigen loss, cerebrospinal fluid lymphocytosis, increased cerebrospinal fluid cell count, blast cell count increased, transformation to acute myeloid leukemia, transplant complication, blast cell count decreased, cytokine release syndrome, and B-cell aplasia.

Table 3
Demographic information of blinatumomab-related ADE reports.

General information	Category	Number of reports (cases)	Composition ratio (%)
Sex	Male	2 700	38.79
	Female	2 312	33.21
	Not reported	1 949	28.00
Age (years)	< 18	838	12.04
	18–44	1 324	19.02
	45–64	1 045	15.01
	≥ 65	676	9.71
	Not reported	3 078	44.22
Top 5 reporting countries	United States	4 001	57.48
	Japan	850	12.21
	Brazil	220	3.16
	Italy	181	2.60
	China	176	2.53
Continent of reporting country	North America	4 172	59.93
	Asia	1 299	18.66
	Europe	994	14.28
	South America	354	5.09
	Oceania	118	1.70
	Africa	24	0.34
Year of report	2014	1	0.01
	2015	401	5.76
	2016	631	9.06
	2017	684	9.83
	2018	646	9.28
	2019	632	9.08
	2020	638	9.17
	2021	840	12.07
	2022	764	10.98
	2023	894	12.84
	2024	830	11.92
Reporter type	Consumer	492	7.07
	Other health professionals	742	10.66
	Pharmacist	2 344	33.67
	Physician	3 377	48.51

SOCs involved in ADE signals

The 290 ADE signals identified after screening, comprising 8010 ADE occurrences, were mapped to their corresponding SOCs in MedDRA. A comparative analysis was then performed to determine whether these ADEs were documented in the blinatumomab's prescribing information. As shown in Table 4, a total of 189 ADE signals were recorded in the prescribing information, whereas 101 signals were not listed. SOCs with relatively high reporting frequencies included nervous system disorders (45 signals, 1573 occurrences), investigations (59 signals, 1107 occurrences), general disorders and administration site conditions (14 signals, 1090 occurrences), immune system disorders (20 signals, 1103 occurrences), blood and lymphatic system disorders (19 signals, 856 occurrences), and infections and infestations (61 signals, 793 occurrences). Detailed distributions are provided in Appendix Table 1.

Table 4
Top 30 preferred terms (PTs) of blinatumomab ADEs ranked by occurrence frequency and signal strength.

PTs with Top 30 Occurrence Frequency	cases	ROR	ROR 95 % CI	PRR	Chi-Square	PTs with Top 30 Signal Strength	cases	ROR	ROR 95 % CI	PRR	Chi-Square
Fever	853	8.43	7.87, 9.03	8.093	5 318.14	Leukemia lineage switch[a]	21	4355.44	2 214.46, 8 566.35	4350.56	36 527.91
Cytokine release syndrome	676	178.91	165.3, 193.61	172.486	108 807.35	CD19 antigen loss[a]	3	1243.22	321.45, 4 808.12	1243.02	2 606.14
Neurotoxicity	399	84.46	76.38, 93.40	82.684	31 313.66	CSF lymphocytosis[a]	7	441.53	199.32, 978.04	441.36	2 669.34
Tremor	198	3.88	3.37, 4.46	3.85	417.44	CSF cell count increased[a]	15	375.35	219.17, 642.80	375.05	4 955.04
Neutropenia	189	4.75	4.11, 5.48	4.71	552.38	primitive blood cell count increased[a]	97	353.05	285.84, 436.08	351.23	30 217.00
Confusional state	166	3.36	2.89, 3.92	3.34	273.14	Transformation to AML[a]	44	266.49	195.64, 363.00	265.87	10 635.52
Seizure	157	2.98	2.55, 3.49	2.97	204.91	Transplant complication	26	238.97	160.16, 356.55	238.64	5 684.99
Infection	155	3.70	3.15, 4.33	3.67	301.85	primitive blood cell count decreased[a]	4	190.23	69.17, 523.19	190.19	706.45
Febrile neutropenia	152	7.84	6.68, 9.20	7.78	896.91	Cytokine release syndrome	676	178.91	165.33, 193.61	172.49	108 807.35
Hypotension	126	2.07	1.74, 2.46	2.06	69.03	B-cell aplasia[a]	8	149.76	73.57, 304.84	149.70	1 123.64
Thrombocytopenia	125	3.75	3.14, 4.47	3.73	250.01	HHV-6 encephalitis	8	113.79	56.14, 230.65	113.74	860.26
Sepsis	114	3.36	2.80, 4.04	3.35	187.66	Oral chronic GVHD[a]	6	104.87	46.44, 236.82	104.83	595.53
Nervous system disorder	108	10.96	9.07, 13.24	10.90	968.05	CD19 lymphocyte decrease	3	104.85	33.13, 331.79	104.83	297.76
Aphasia	99	10.47	8.59, 12.76	10.42	840.50	Bone marrow necrosis[a]	7	100.55	47.32, 213.64	100.51	666.53
primitive blood cell increased[a]	97	353.05	285.84, 436.08	351.23	30 217.00	Neurotoxicity	399	84.46	76.38, 93.40	82.68	31 313.66
Platelet count decreased	95	2.93	2.40, 3.59	2.92	120.24	Transient aphasia	3	82.88	26.30, 261.16	82.87	235.90
Pancytopenia	90	5.40	4.39, 6.64	5.38	320.82	Ocular GVHD[a]	5	81.49	33.50, 198.22	81.47	386.56
Hepatotoxicity	85	13.09	10.57, 16.21	13.04	940.77	Ocular chronic GVHD[a]	4	78.94	29.23, 213.15	78.92	299.59
Leukocyte count decreased	77	2.32	1.86, 2.91	2.32	57.84	Cutaneous GVHD[a]	42	65.36	48.12, 88.77	65.21	2 597.24
Neutrophil count decreased	77	6.51	5.20, 8.14	6.49	356.81	Hepatic GVHD[a]	12	58.83	33.21, 104.20	58.79	668.16
Encephalopathy	74	10.06	8.01, 12.65	10.03	599.64	Infusion site hemorrhage	50	58.75	44.39, 77.76	58.59	2 774.60
ALT increased	70	3.70	2.92, 4.68	3.69	137.03	ICANS	65	57.64	45.07, 73.71	57.44	3 535.06
Acute GVHD[a]	70	50.39	39.77, 63.85	50.20	3 318.51	Cutaneous chronic GVHD[a]	14	55.89	32.93, 94.87	55.85	739.95
Tachycardia	69	2.56	2.02, 3.24	2.55	65.07	Gastrointestinal GVHD[a]	36	54.94	39.50, 76.43	54.84	1 867.61
Adverse event	67	2.40	1.89, 3.05	2.40	54.56	Veno-occlusive disease[a]	42	54.72	40.31, 74.28	54.60	2 169.28
GVHD	66	29.96	23.50, 38.20	29.86	1 822.35	Chloroma	7	54.02	25.57, 114.10	54.00	357.45
ICANS	65	57.64	45.07, 73.71	57.44	3 535.06	Device-related bacteremia	4	52.99	19.71, 142.46	52.97	200.32
Myelosuppression	61	8.32	6.47, 10.70	8.30	390.62	Cutaneous acute GVHD[a]	41	52.64	38.64, 71.71	52.52	2 035.51
Tumor lysis syndrome	59	23.57	18.24, 30.47	23.50	1 261.11	Fibrin degradation products increased[a]	5	52.37	21.62, 126.82	52.35	247.40
AST increased	56	3.41	2.62, 4.43	3.40	95.04	Acute GVHD[a]	70	50.39	39.77, 63.85	50.20	3 318.51

[a] Not listed in the prescribing information. GVHD, graft-versus-host disease; ICANS, immune effector cell-associated neurotoxicity syndrome; AST, aspartate amino transferase; CSF, cerebrospinal fluid; AML, acute myelogenous leukemia; HHV-6, human herpesvirus type 6.

Table 5
Influencing factors for ADEs in the total population and different age groups.

Category	Group	Total population cases (%)	Juveniles cases (%)	Middle-aged adults cases (%)	Elderly cases (%)	P-value (between groups)
Cases	-	8010	1280	3041	895	-
Sex	Male	3 448 (55.0)	696 (57.2)	1662 (56.5)	426 (49.1)	< 0.001
	Female	2 817 (45.0)	520 (42.8)	1281 (43.5)	441 (50.9)	
Body Weight	< 80 kg	1136 (75.0)	378 (90.2)	517 (69.9)	197 (64.4)	< 0.001
	≥ 80 kg	379 (25.0)	41 (9.8)	223 (30.1)	109 (35.6)	
Interval time	0–7 days	1667 (70.3)	391 (72.5)	723 (67.6)	294 (66.2)	< 0.001
	8–15 days	200 (8.4)	22 (4.1)	104 (9.7)	38 (8.6)	
	16–30 days	172 (7.3)	28 (5.2)	107 (10.0)	32 (7.2)	
	≥ 31 days	333 (14.0)	98 (18.2)	136 (12.7)	80 (18.0)	
Continent	North America	3732 (46.8)	439 (34.6)	1469 (48.7)	435 (48.9)	<0.001
	Europe	1582 (19.8)	273 (21.5)	672 (22.2)	148 (16.7)	
	Asia	2056 (25.8)	383 (30.1)	652 (21.6)	282 (31.7)	
	Other regions	601 (7.5)	175 (13.8)	226 (7.5)	24 (2.7)	

Note: P values indicate comparisons among juveniles, middle-aged adults, and elderly groups. In the "Interval time" and "Continent" categories, pairwise comparisons between subgroups showed statistically significant differences.

Signal analysis

The prescribing information[2] specifically includes a boxed warning for the severe and potentially fatal toxicities of cytokine release syndrome (CRS) and neurotoxicity. Among all adverse events, neurotoxicity and infections are the most common causes leading to treatment discontinuation with blinatumomab. The prescribing information also notes that blood and lymphatic system disorders, immune system disorders, infections and infestations, and nervous system disorders are either very common (incidence ≥10 %) or grade 3 or higher adverse events with an incidence ≥ 5 %. The distribution of high-frequency ADEs identified in this signal detection analysis was generally consistent with those listed in the prescribing information. Our analysis identified leukemia lineage switch as the ADE with the strongest signal strength for blinatumomab. Transformation to acute myeloid leukemia, ranked sixth in signal strength, also belongs to the category of lineage switch. The combined occurrence of these two ADEs was only 65 reports. Notably, lineage switch is not mentioned in the prescribing information, suggesting it is a rare but strongly drug-associated adverse event that warrants close clinical attention.

In this study, we focused on six categories of ADEs associated with blinatumomab, including neurological disorders, CRS, immune system disorders, blood and lymphatic system disorders, infections and infestations, and lineage switch. For each category, comparative analyses were conducted across patient age (minors (< 18 years), adults (18–64 years), and elderly patients (≥65 years)), influencing factors (age, sex, body weight, time interval from drug administration to ADE onset (hereafter referred to as "time interval"), continent of patient origin (hereafter referred to as "continent"), and ADE category. The results of the influencing factor analysis for ADE occurrence in different age groups are presented in Table 5. Comparisons of influencing factors between organ system-specific ADEs and other ADEs are shown in Table 6. Comparisons between minors and adults for each organ system-specific ADE category are provided in Table 7, and comparisons between elderly and non-elderly patients are provided in Table 8.

Analysis of influencing factors for AEs in the overall and age-stratified populations

In the overall population reporting AEs associated with blinatumomab, the proportion of male patients was higher, with a male-to-female ratio of 1.22:1. Most patients weighed ≤ 80 kg (75 %). AEs primarily occurred within 0–7 days after administration (70.3 %), followed by events occurring after more than 31 days (14 %). The continent with the highest number of reports was North America (46.8 %), followed by Asia (25.8 %) and Europe (19.8 %). In age-stratified analyses, elderly female patients accounted for a high proportion of AEs (50.9 %). Among minors, body weight was more frequently ≤ 80 kg (90.2 %). Compared with the overall population, minors were more likely to experience delayed AEs occurring more than 31 days after administration (18.2 %). Both Asian minors and elderly patients had relatively higher proportions of AEs compared with the middle-aged counterparts.

Comparison of influencing factors between system-specific adverse events and other adverse events

In terms of time interval, neurological and infection-related adverse events tended to occur later, with a higher proportion of cases arising more than 7 days after administration. In contrast, CRS occurred relatively early, with 83.5 % of cases reported within 0–7 days. Hematologic and lymphatic system disorders showed a relatively high proportion of onset between 16 and 30 days after administration (12.2 %). Regarding the continent of patient origin, the proportion of CRS, immune system disorders, and hematologic and lymphatic system disorders was higher among Asian patients, whereas the proportion of neurological disorders and infection-related adverse events was higher among European patients.

Comparison of influencing factors for system-specific AEs between minors and adults

In terms of gender, juvenile males showed a higher proportion of CRS and immune system disorders compared with adult males. In terms of body weight, most juveniles experiencing AEs weighed less than 80 kg, which was generally lower than that of adults. Regarding time interval, neurological adverse events in juveniles tended to occur either earlier or later, with the majority reported within 0–7 days (70.2 %), followed by those occurring after more than 31 days (19.2 %). By continent of patient origin, Asian juveniles had a relatively higher proportion of neurological disorders and infection-related AEs.

Comparison of influencing factors for system-specific AEs between elderly and non-elderly patients

Compared with non-elderly patients, elderly females experiencing neurological disorders, hematologic and lymphatic system disorders had a higher proportion of body weight ≥ 80 kg. By continent of patient origin, Asian elderly patients exhibited a relatively higher proportion of neurological disorders, immune system disorders, hematologic and lymphatic system disorders, and infection-related AEs.

Discussion

Blinatumomab has been approved globally for indications covering patients of all ages, resulting in a wide age range among treated

Table 6
Comparison of the influencing factors between ADEs in various organ systems and other ADEs.

Category	Group	Neurologic ADEs cases (%)	Other ADEs cases (%)	P-value	CRS cases (%)	Other CRS cases (%)	P-value	Immune system ADEs cases (%)	Other ADEs cases (%)	P-value
Age	Juvenile	229 (23.5)	1051 (24.8)	0.144	108 (26.0)	1172 (24.4)	0.740	195 (28.1)	1085 (24.0)	< 0.001
	Middle-aged adults	559 (57.3)	2482 (58.5)		239 (57.6)	2802 (58.4)		414 (59.7)	2627 (58.1)	
	Elderly	188 (19.2)	707 (16.7)		68 (16.4)	827 (17.2)		85* (12.2)	810 (17.9)	
Sex	Male	656 (52.6)	2792 (55.7)	0.052	287 (54.2)	3161 (55.1)	0.669	455 (54.9)	2993 (55.1)	0.925
	Female	592 (47.4)	2225 (44.3)		243 (45.8)	2574 (44.9)		374 (45.1)	2443 (44.9)	
Body weight	< 80 kg	238 (76.0)	898 (74.7)	0.629	94 (81.7)	1042 (74.4)	0.082	117 (79.6)	1019 (74.5)	0.175
	≥ 80 kg	75 (24.0)	304 (25.3)		21 (18.3)	358 (25.6)		30 (20.4)	349 (25.5)	
Interval time	0–7 days	299* (63.8)	1368 (71.9)	0.002	177* (83.5)	1490 (69.0)	< 0.001	203 (75.5)	1464 (69.6)	0.266
	8–15 days	57* (12.1)	143 (7.5)		14 (6.6)	186 (8.6)		18 (6.7)	182 (8.7)	
	16–30 days	39 (8.3)	133 (7.0)		8 (3.8)	164 (7.6)		16 (5.9)	156 (7.4)	
	≥ 31 days	74 (15.8)	259 (13.6)		13* (6.1)	320 (14.8)		32 (11.9)	301 (14.3)	
Continent	North America	829 (53.5)	2903 (45.2)	< 0.001	288 (42.3)	3444 (47.2)	< 0.001	403 (36.6)	3329 (48.5)	< 0.001
	Europe	364 (23.5)	1218 (19.0)		93 (13.7)	1489 (20.4)		207 (18.8)	1375 (20.0)	
	Asia	235* (15.2)	1821 (28.4)		267* (39.2)	1789 (24.5)		432* (39.3)	1624 (23.6)	
	Other regions	122 (7.9)	479 (7.5)		33 (4.8)	568 (7.8)		58 (5.3)	543 (7.9)	
Age	Juvenile	144 (24.7)	1136 (24.5)	0.695	105 (23.8)	1175 (24.6)	0.482	11 (28.2)	1269 (24.5)	0.856
	Middle-aged adults	347 (59.4)	2694 (58.2)		268 (60.8)	2773 (58.1)		22 (56.4)	3019 (58.3)	
	Elderly	93 (15.9)	802 (17.3)		68 (15.4)	827 (17.3)		6 (15.4)	889 (17.2)	
Sex	Male	354 (55.1)	3094 (55.0)	0.996	284 (54.3)	3164 (55.1)	0.725	21 (46.7)	3427 (55.1)	0.257
	Female	289 (44.9)	2528 (45.0)		239 (45.7)	2578 (44.9)		24 (53.3)	2793 (44.9)	
Body weight	< 80 kg	117 (72.2)	1019 (75.3)	0.391	91 (77.1)	1045 (74.8)	0.577	4 (100.0)	1132 (74.9)	0.563
	≥ 80 kg	45 (27.8)	334 (24.7)		27 (22.9)	352 (25.2)		0 (0.0)	379 (25.1)	
Interval time	0–7 days	155* (67.7)	1512 (70.6)	0.013	92* (55.1)	1575 (71.4)	< 0.001	4 (57.1)	1663 (70.3)	0.216
	8–15 days	21 (9.2)	179 (8.4)		11# (6.6)	189 (8.6)		0 (0.0)	200 (8.5)	
	16–30 days	28*# (12.2)	144 (6.7)		17 (10.2)	155 (7.0)		0 (0.0)	172 (7.3)	
	≥ 31 days	25# (10.9)	308 (14.4)		47*# (28.1)	286 (13.0)		3 (42.9)	330 (14.0)	
Continent	North America	318*# (37.2)	3414 (48.0)	< 0.001	355 (44.9)	3377 (47.0)	< 0.001	31 (47.7)	3701 (46.8)	0.209
	Europe	218* (25.5)	1364 (19.2)		208* (26.3)	1374 (19.1)		18 (27.7)	1564 (19.8)	
	Asia	248# (29.0)	1808 (25.4)		179 (22.6)	1877 (26.1)		14 (21.5)	2042 (25.8)	
	Other regions	71 (8.3)	530 (7.4)		49 (6.2)	552 (7.7)		2 (3.1)	599 (7.6)	

Notes: Intergroup differences in each category are indicated by * and #. For variables with ≥ 2 groups, one * indicates that this group shows statistically significant differences when compared pairwise with all other groups. For variables with ≥ 2 groups, two identical symbols (* or #) indicate that the two groups marked with the same symbol are significantly different from each other.

Table 7
Comparison of influencing factors for ADEs in various SOCs between minors and adults.

Category	Group	Adult neurologic ADEs cases (%)	Minor neurologic ADEs cases (%)	P-value	Adult CRS cases (%)	Minor CRS cases (%)	P-value	Adult immune system ADEs cases (%)	Minor immune system ADEs cases (%)	P-value
Sex	Male	365 (51.7)	131 (58.5)	0.076	150 (51.0)	66 (64.1)	0.022	253 (52.4)	115 (61.2)	0.04
	Female	341 (48.3)	93 (41.5)		144 (49.0)	37 (35.9)		230 (47.6)	73 (38.8)	
Body weight	<80 kg	140 (67.0)	89 (95.7)	<0.001	62 (78.5)	30 (90.9)	0.117	79 (75.2)	35 (92.1)	0.027
	≥80 kg	69 (33.0)	4 (4.3)		17 (21.5)	3 (9.1)		26 (24.8)	3 (7.9)	
Interval time	0-7 days	184* (59.7)	73 (70.2)	0.015	103 (80.5)	32 (82.1)	0.473	126 (72.0)	35 (71.4)	0.594
	8–15 days	43*# (14.0)	3 (2.9)		11 (8.6)	1 (2.6)		14 (8.0)	2 (4.1)	
	16-30 days	29 (9.4)	8 (7.7)		6 (4.7)	2 (5.1)		13 (7.4)	3 (6.1)	
	≥31 days	52# (16.9)	20 (19.2)		8 (6.3)	4 (10.2)		22 (12.6)	9 (18.4)	
Continent	North America	388*# (53.1)	83 (37.4)	<0.001	115 (37.6)	32 (30.0)	0.512	154 (30.9)	49 (25.3)	0.105
	Europe	194 (26.5)	63 (28.4)		48 (15.7)	21 (19.6)		116 (23.3)	37 (19.1)	
	Asia	97* (13.3)	43 (19.4)		126 (41.2)	48 (44.9)		205 (41.2)	100 (51.5)	
	Other regions	52# (7.1)	33 (14.9)		17 (5.5)	6 (5.6)		23 (4.6)	8 (4.1)	
Sex	Male	233 (54.3)	75 (52.0)	0.133	179 (54.7)	54 (53.5)	0.822	12 (44.4)	6 (60.0)	0.638
	Female	196 (45.7)	46 (38.0)		148 (45.3)	47 (46.5)		15 (55.6)	4 (40.0)	
Body weight	<80 kg	83 (65.4)	31 (96.9)	<0.001	63 (70.8)	23 (95.8)	0.011	3 (100.0)	1 (100.0)	-
	≥80 kg	44 (34.6)	1 (3.1)		26 (29.2)	1 (4.2)		0 (0.0)	0 (0.0)	
Interval time	0-7 days	104 (64.2)	31 (72.1)	0.299	66 (56.9)	14 (43.8)	0.111	0 (0.0)	2 (66.7)	-
	8–15 days	16 (9.9)	1 (2.3)		9 (7.8)	0 (0.0)		0 (0.0)	0 (0.0)	
	16-30 days	23 (14.2)	5 (11.6)		12 (10.3)	5 (15.6)		0 (0.0)	0 (0.0)	
	≥31 days	19 (11.7)	6 (14.0)		29 (25.0)	13 (40.6)		2 (100.0)	1 (33.3)	
Continent	North America	168* (38.3)	37 (25.7)	0.007	145* (43.4)	31 (29.5)	0.004	19 (67.9)	6 (54.5)	0.334
	Europe	119 (27.1)	46 (31.9)		93 (27.8)	24 (22.9)		5 (17.9)	1 (9.1)	
	Asia	118 (26.9)	39 (27.1)		74* (22.2)	38 (36.2)		3 (10.7)	4 (36.4)	
	Other regions	34* (7.7)	22 (15.3)		22 (6.6)	12 (11.4)		1 (3.6)	0 (0.0)	

Notes: Intergroup differences in each category are indicated by * and #. For variables with ≥2 groups, one * indicates that this group shows statistically significant differences when compared pairwise with all other groups. For variables with ≥2 groups, two identical symbols (* or #) indicate that the two groups marked with the same symbol are significantly different from each other.

Table 8
Comparison of influencing factors for ADEs in various SOCs between the elderly and the non-elderly.

Category	Group	Non-elderly neurologic ADEs cases (%)	Elderly neurologic ADEs cases (%)	P-value	Non-elderly CRS cases (%)	Elderly CRS cases (%)	P-value	Non-elderly immune system ADEs cases (%)	Elderly immune system ADEs cases (%)	P-value
Sex	Male	409 (54.2)	87 (49.7)	0.287	186 (56.4)	30 (44.8)	0.083	330 (56.2)	38 (45.2)	0.059
	Female	346 (45.8)	88 (50.3)		144 (43.6)	37 (55.2)		257 (43.8)	46 (54.8)	
Body weight	<80 kg	182 (79.1)	47 (65.3)	0.017	81 (84.4)	11 (68.8)	0.247	99 (82.5)	15 (65.2)	0.108
	≥80 kg	48 (20.9)	25 (34.7)		15 (15.6)	5 (31.3)		21 (17.5)	8 (34.8)	
Interval time	0-7 days	200 (63.1)	57 (60.0)	0.288	111 (80.4)	24 (82.8)	0.129	133 (71.9)	28 (71.8)	0.511
	8–15 days	34 (10.7)	12 (12.6)		11 (8.0)	1 (3.4)		15 (8.1)	1 (2.6)	
	16-30 days	32 (10.1)	5 (5.3)		8 (5.8)	0 (0.0)		13 (7.0)	3 (7.7)	
	≥31 days	51 (16.1)	21 (22.1)		8 (5.8)	4 (13.8)		24 (13.0)	7 (17.9)	
Continent	North America	365* (47.4)	106 (57.9)	0.001	124 (35.8)	23 (34.3)	0.004	176 (28.9)	27 (32.1)	0.005
	Europe	223*# (29.0)	34 (18.6)		62* (17.9)	7 (10.4)		144* (23.7)	9 (10.7)	
	Asia	106# (13.8)	34 (18.6)		137*# (39.6)	37 (55.2)		258* (42.4)	47 (56.0)	
	Other regions	76 (9.9)	9 (4.9)		23# (6.6)	0 (0.0)		30 (4.9)	1 (1.2)	
Sex	Male	258 (56.5)	50 (53.8)	0.634	200 (55.4)	33 (49.3)	0.353	15 (48.4)	3 (50.0)	1
	Female	199 (43.5)	43 (46.2)		161 (44.6)	34 (50.7)		16 (51.6)	3 (50.0)	
Body weight	<80 kg	93 (76.9)	21 (55.3)	0.01	71 (77.2)	15 (71.4)	0.577	4 (100.0)	0 (0.0)	—
	≥80 kg	28 (23.1)	17 (44.7)		21 (22.8)	6 (28.6)		0 (0.0)	0 (0.0)	
Interval time	0-7 days	106 (67.5)	29 (60.4)	0.605	63 (53.8)	17 (54.8)	0.877	2 (40.0)	0 (0.0)	—
	8–15 days	11 (7.0)	6 (12.5)		8 (6.8)	1 (3.2)		0 (0.0)	0 (0.0)	
	16-30 days	22 (14.0)	6 (12.5)		13 (11.1)	4 (12.9)		0 (0.0)	0 (0.0)	
	≥31 days	18 (11.5)	7 (14.6)		33 (28.2)	9 (29.0)		3 (60.0)	0 (0.0)	
Continent	North America	168 (34.3)	37 (39.8)	0.013	152 (41.0)	24 (35.3)	0.02	21 (63.6)	4 (66.7)	0.381
	Europe	147* (30.0)	18 (19.4)		102 (27.5)	15 (22.1)		4 (12.1)	2 (33.3)	
	Asia	123*# (25.1)	34 (36.6)		85* (22.9)	27 (39.7)		7 (21.2)	0 (0.0)	
	Other regions	52# (10.6)	4 (4.3)		32 (8.6)	2 (2.9)		1 (3.0)	0 (0.0)	

Notes: Intergroup differences in each category are indicated by * and #. For variables with ≥2 groups, one * indicates that this group shows statistically significant differences when compared pairwise with all other groups. For variables with ≥2 groups, two identical symbols (* or #) indicate that the two groups marked with the same symbol are significantly different from each other.

individuals. This necessitates age-stratified analyses of drug-related AEs and targeted pharmaceutical monitoring for different age groups. Current clinical trial data and real-world evidence suggest discrepancies in the safety profile of blinatumomab between adult and pediatric populations.[11–14] In real-world settings, adults generally exhibit lower incidences of neurotoxicity, CRS, infections, hematologic toxicities, grade ≥ 3 AEs, and overall AE occurrence compared with clinical trial reports. In contrast, real-world safety data for pediatric patients remain scarce. Moreover, existing real-world studies are geographically limited, with most analyses based on specific regional populations.[13,14] Given the recent introduction of blinatumomab in China and the limited domestic clinical experience, a broader, age-stratified safety evaluation in real-world patient populations is warranted.

Characteristics of blinatumomab-associated AEs

According to the prescribing information, the median time to onset of neurological adverse events in adults is 9 days.[2] Similarly, our signal detection analysis found that a relatively higher proportion of neurological AEs occurred more than 7 days after drug administration, indicating a tendency toward delayed onset. Therefore, pharmaceutical monitoring should pay particular attention to delayed neurological AEs associated with blinatumomab. Neurological AEs, particularly immune effector cell-associated neurotoxicity syndrome (ICANS), represent one of the most characteristic toxicities of blinatumomab. The pathogenesis of ICANS is not fully understood. Studies suggest that it is related to cytokine-induced neuroinflammation and endothelial activation, disruption of the blood–brain barrier and direct neuronal injury. Early manifestations of ICANS include expressive aphasia, tremor, and writing difficulty, which can progress to seizures, decreased consciousness, encephalopathy, coma, and, in severe cases, cerebral edema. Although according to several studies, no significant association has been found between CRS and the occurrence of neurological events, several factors have been identified as risk factors for neurotoxicity, including advanced age, a history of preexisting neurological symptoms, non-Caucasian ethnicity, and more than twice therapies after relapse.[15–17] In contrast, no clear association has been observed with dose or tumor burden. For patients receiving blinatumomab for the first time, before dose escalation, or when restarting therapy, glucocorticoid premedication is recommended. If seizures occur during treatment, symptomatic management with levetiracetam or phenytoin sodium may be considered; however, routine prophylactic use of antiepileptic drugs is not recommended.[2,18,19]

In both CRS and immune system-related AEs, the proportion of Asian patients was relatively higher, and CRS tended to present as an early-onset event. CRS is a severe systemic inflammatory response syndrome triggered by the activation of immune cells and subsequent release of large quantities of cytokines. The mechanism of CRS induced by blinatumomab involves the initiation of antigen–antibody interactions, which activate cytotoxic T cells and, in turn, stimulate macrophages and monocytes. This activation process occurs rapidly, leading to the release of a large number of cytokines within a short period. Through cascade amplification, cytokine concentrations can increase sharply in a short time, resulting in rapid onset of AEs.[20] The median time to CRS onset is 1–2 days. Studies have identified high tumor burden, initial dosing, and advanced age as major risk factors for CRS.[15] Therefore, patients with high tumor burden should receive pre-phase treatment with dexamethasone, and glucocorticoid premedication should be administered before the first dose, dose escalation, or re-initiation of infusion. Close monitoring for CRS reactions in the early period after administration is essential, as early prevention and recognition are critical. Once CRS occurs, prompt administration of corticosteroids for symptomatic management is recommended to reduce the risk of severe CRS.[21]

In hematologic and lymphatic system-related AEs, the proportion of cases occurring within 16–30 days after administration was relatively high, with Asian patients accounting for a larger proportion. The primary hematologic AEs associated with blinatumomab include neutropenia and febrile neutropenia. Mechanistically, taking neutropenia as an example, blinatumomab can induce an immune response, leading to the production of antibodies that recognize and bind to antigens on the surface of neutrophils. This process activates the complement system, resulting in phagocytosis and destruction of neutrophils. Additionally, blinatumomab can interfere with the normal proliferation and differentiation of hematopoietic stem cells in the bone marrow, preventing neutrophil precursors from maturing into functional neutrophils, thereby reducing peripheral neutrophil counts. Moreover, blinatumomab may activate intracellular apoptotic signaling pathways, further contributing to neutrophil depletion.[22] Notably, the complete maturation cycle of neutrophils, from differentiation in the bone marrow to their release into peripheral circulation, typically requires approximately 10–14 days.[23]

The increased risk of infection associated with blinatumomab is primarily attributable to its ability to induce B-cell depletion and to reduce immunoglobulin levels during and after treatment, thereby increasing susceptibility to infections. In such cases, immunoglobulin replacement therapy, via intravenous immunoglobulin infusion, can be considered as a management approach. Since a relatively high proportion of infection events occurred more than seven days after administration, it is important to enhance patient follow-up and conduct timely monitoring of relevant clinical parameters.[24]

Due to the low frequency of lineage switch events, no statistically significant differences between groups were identified in the present risk factor analysis. Further investigation will require the accumulation of more reported cases. Lineage switch primarily involves changes in the immunophenotype of leukemic cells, with the most typical example being the transformation of BCP-ALL into acute myeloid leukemia (AML). This phenomenon may result from a combination of tumor cell plasticity, immune selection, and alterations in the bone marrow microenvironment, which together promote extensive genetic diversification and subsequent clonal selection, ultimately leading to lineage switching as a mechanism of treatment escape.[25,26]

Risk factors associated with blinatumomab AEs

Across the evaluated risk factors, differences in sex and body weight aligned with general demographic patterns and the physiological principles of human growth and development. The higher proportion of AEs in elderly females may be related to their longer average life expectancy compared with men. The relatively lower body weight in pediatric patients is consistent with their stage of ongoing physical growth and development.

(1) Asian population

Compared with other continents, the proportion of CRS, immune system disorders, and hematologic and lymphatic system disorders was higher among Asian patients, particularly within the pediatric and elderly subgroups. These groups demonstrated reduced drug tolerance and increased susceptibility to AEs, suggesting the need for heightened monitoring in clinical practice. This may be partly attributable to differences in genetic background, lifestyle, and environmental exposures. For example, certain *CYP2C19* polymorphisms, which are more prevalent in Asian populations, have been associated with reduced enzyme activity.[27] Such genetic variations can slow the metabolism of drugs metabolized by this enzyme, increasing systemic exposure and the risk of AEs. Given these factors, blinatumomab administration in Asian populations should be accompanied by enhanced AE surveillance.

(2) Minors

Overall, minor patients treated with blinatumomab were more likely to develop delayed-onset AEs. This may be related to the immaturity of T-cell function and incomplete development of T-cell antigen recognition capacity and signal transduction pathways, which together create an unstable immune state that increases the risk of delayed AEs following drug stimulation.[28] In addition, minor patients

have reduced physiological adaptability to prolonged drug exposure, which may lead to cumulative effects and delayed toxicity.

Notably, although neurologic AEs tended to be delayed in the overall population, minor patients experienced neurologic AEs earlier in the treatment course, consistent with clinical trial findings.[17,29] This may be related to the developmental status of the nervous system, the higher permeability of the blood–brain barrier in children, and the greater ease with which drugs or immune mediators (e.g., cytokines) can cross into the central nervous system. The heightened sensitivity and reduced self-regulatory capacity of the pediatric immune system may also predispose this population to rapid immune overactivation that affects the nervous system, leading to rapid neurological AEs.[30] Therefore, both early- and delayed-onset neurologic AEs warrant close monitoring in these patients, and initial neurologic symptoms should prompt early intervention, such as corticosteroid administration.

The proportion of CRS and immune system events was higher in male minor patients compared with females. The more active immune profile in children, combined with potentially higher T-cell activity in males, may increase the risk of excessive immune activation following blinatumomab administration.[31] Moreover, males generally have higher total body fluid volumes and greater lean muscle mass than females, factors that may influence the drug's volume of distribution and tissue kinetics, possibly prolonging immune system stimulation and the duration of pharmacological effects.

(3) Elderly patients

The proportion of immune system events was relatively lower in elderly patients. This may reflect immunosenescence, the age-associated decline in immune function, characterized by reduced immune cell activity and numbers, as well as diminished T-cell responsiveness.[32] In addition, age-related changes in cytokine production and regulation may attenuate the amplification cascade required for severe immune-mediated events, making it less likely for elderly patients to develop high-grade immune system AEs following blinatumomab therapy.

Clinical implications of the presents signal detection findings

From the overall demographic distribution of reported blinatumomab AEs, sex, body weight, and age proportions were generally consistent with global population patterns. The time-to-onset of AEs after drug administration was also largely consistent with the prescribing information and previously published studies. However, the geographic distribution of AE reports differed from global population distribution, with the majority originating from North America, followed by Asia and Europe. Possible explanations include: (1) accessibility, differences in the timing of blinatumomab market approval across countries; (2) economic factors, variation in patient income levels and national health insurance coverage [33]; and (3) reporting bias.[34] All three factors may have influenced the global utilization and reporting patterns of blinatumomab.

In summary, during blinatumomab therapy, appropriate premedication should be implemented, particularly corticosteroid pretreatment for patients with high tumor burden. Close attention should be paid to drug tolerance in Asian patients, strengthened continuous AE monitoring for pediatric and elderly patients is warranted. Special attention should be given to CRS and immune-related AE surveillance, as well as to the management of neurologic toxicities. Both early-onset and delayed-onset AEs warrant careful monitoring, with vigilance for early neurologic symptoms to enable timely intervention.

Comparison of AEs in domestic and international patient populations

According to literature reports, the AE profile of blinatumomab in Chinese patients differs in certain aspects from international findings. In a single-center retrospective study in China, 78.6 % of patients experienced fever and 28.6 % had elevated transaminases following blinatumomab treatment, both higher than the corresponding rates reported in the TOWER study (59.6 % and 12.7 %, respectively). Moreover, the incidence of anemia and thrombocytopenia in Chinese patients (42.9 % and 35.7 %) exceeded that observed internationally, suggesting a potentially higher risk of bone marrow suppression in Chinese.[35,36] A case report has also described neurological toxicities in Chinese pediatric patients, such as trigeminal neuralgia and headache, with incidence rates similar to those in international studies (23 %) and no fatal events observed, indicating an overall manageable safety profile.[37]

Currently, research on blinatumomab-related AEs in the Chinese population remains limited to small-sample studies, partly due to its relatively recent approval in mainland China (December 2020). These studies may be subject to selection bias. Future research should aim to optimize treatment regimens for Chinese patients by considering specific disease characteristics, such as high tumor burden and immune status, and to conduct multicenter studies that generate robust evidence. Such efforts will provide a stronger scientific basis for the standardized clinical use of blinatumomab in China.

Limitations of the study

This study has several limitations. The data were derived from a spontaneous reporting database, which is inherently subject to bias, and the quality and completeness of the reports may be suboptimal. Most reports in the FAERS database originate from Europe and North America, with a relatively low proportion from the Chinese population. Therefore, the signal detection results may not fully reflect the real-world situation in China. Furthermore, the detection of positive signals only indicates statistical associations. Establishing a true causal relationship requires further evaluation and confirmation through appropriately designed clinical studies. Signal strength can only suggest the relative magnitude of risk and should not be interpreted as an absolute quantification of risk. Future research should include prospective clinical trials and real-world studies to further clarify the safety profile of blinatumomab in Chinese patients.

Perspectives and outlook

At present, the clinical use of novel antitumor agents introduced into China, including blinatumomab, remains largely guided by the dosage and administration recommendations specified in the prescribing information from the original marketing countries. However, dose-related toxicities and suboptimal dosing regimens may, to some extent, limit the proportion of Chinese patients who can benefit. It is therefore necessary to actively conduct clinical trials targeting Asian populations, particularly Chinese patients, to explore dose-safety-efficacy relationships.[38] Optimizing dosing strategies to balance efficacy and risk will help establish a tailored regimen that ensures safety while maximizing therapeutic benefit.

Due to the inherent limitations of data collected in the FAERS database, the present analysis was unable to capture certain clinical variables, including comorbidities, prior adverse events, disease stage or tumor burden, treatment lines, concomitant medications, detailed AE onset timelines, and AE duration. Our research team plans to address these gaps in future work by conducting real-world studies specifically in the Chinese population. These studies will incorporate the currently missing information, focusing on the safety and efficacy of blinatumomab in Chinese patients, with the goal of providing an evidence-based, China-specific dosing and monitoring strategy.

Declarations

Not applicable.

Authors' contributions

Jinglin Liu: Data curation, Formal analysis, Investigation, Visualization, Writing-original draft. **Xiaokun Song:** Writing-review & editing. **Jie Zhang:** Writing-review & editing. **Bole Li:** Project administration, Supervision, Writing-review & editing. All authors contributed to the article and approved the submitted version.

Ethics approval and consent to participate

As the study utilized publicly accessible databases, there was no requirement for ethics committee approval or informed consent from participants. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

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Declarations of Competing Interests

The authors declare that they have no competing interests.

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Authors' other information

Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prmedi.2025.100065.

References

1. FDA. FDA granted accelerated approval to blinatumomab (Blincyto, Amgen Inc.) for the treatment of adult and pediatric patients with B-cell precursor acute lymphoblastic leukemia [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2018 Mar 29 [cited 2025 Apr 6]. Available from: 〈https://www.fda.gov/drugs/resources-information-approved-drugs/fda-granted-accelerated-approval-blinatumomab-blincyto-amgen-inc-treatment-adult-and-pediatric〉.
2. Blinatumomab for injection prescribing information [Internet]. Beijing: National Healthcare Security Administration; 2023 May 15 [cited 2025 Apr 6]. Chinese. Available from: 〈https://www.nhsa.gov.cn/attach/Ypsn2025/YPSW202500368/YPSW202500368〉(ppt).pdf.
3. Brown PA, Ji L, Xu X, et al. Effect of Postreinduction Therapy Consolidation With Blinatumomab vs Chemotherapy on Disease-Free Survival in Children, Adolescents, and Young Adults With First Relapse of B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. *JAMA*. 2021;325(9):833–842. https://doi.org/10.1001/jama.2021.0669
4. Locatelli F, Zugmaier G, Mergen N, et al. Blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia: results of the RIALTO trial, an expanded access study. *Blood Cancer J.* 2020;10(7):77. https://doi.org/10.1038/s41408-020-00342-x
5. Li YM, Sun XM, Qi PJ, et al. Safety analysis and pharmaceutical care of blinatumomab in the treatment of childhood acute lymphoblastic leukemia. *J Pedia Pharm.* 2024;30(8):12–16. https://doi.org/10.13407/j.cnki.jpp.1672-108X.2024.08.003
6. Ma J, Zhao DL. Interpretation of "Chinese expert consensus on bispecific T-cell engager therapy for acute lymphoblastic leukemia (2024 edition)". *J Clin Hematol.* 2024;37(11):755–758. https://doi.org/10.13201/j.issn.1004-2806.2024.11.001
7. U.S. Food and Drug Administration. FDA Adverse Event Reporting System (FAERS) quarterly data extract files [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; [cited 2025 Oct 23]. Available from:〈https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/faers-quarterly-data-files-documentation〉.
8. Sakaeda T, Tamon A, Kadoyama K, et al. Data mining of the public version of the FDA Adverse Event Reporting System. *Int J Med Sci.* 2013;10(7):796–803. https://doi.org/10.7150/ijms.6048
9. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharm.* 1998;54(4):315–321. https://doi.org/10.1007/s002280050466
10. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf.* 2001;10(6):483–486. https://doi.org/10.1002/pds.677
11. Locatelli F, Maschan A, Boissel N, et al. Pediatric patients with acute lymphoblastic leukemia treated with blinatumomab in a real-world setting: results from the NEUF study. *Pedia Blood Cancer.* 2022;69(4):e29562. https://doi.org/10.1002/pbc.29562
12. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med.* 2017;376(9):836–847. https://doi.org/10.1056/NEJMoa1609783
13. Boissel N, Chiaretti S, Papayannidis C, et al. Real-world use of blinatumomab in adult patients with B-cell acute lymphoblastic leukemia in clinical practice: results from the NEUF study. *Blood Cancer J.* 2023;13(1):2. https://doi.org/10.1038/s41408-022-00766-7
14. Zhou H, Wu X, Yang Z, et al. Real-world evidence on treatment pattern, effectiveness, and safety of blinatumomab in Chinese patients with B-cell acute lymphoblastic leukemia. *Invest N Drugs.* 2024;42(3):299–308. https://doi.org/10.1007/s10637-024-01435-1
15. Mocquot P, Mossazadeh Y, Lapierre L, et al. The pharmacology of blinatumomab: state of the art on pharmacodynamics, pharmacokinetics, adverse drug reactions and evaluation in clinical trials. *J Clin Pharm Ther.* 2022;47(9):1337–1351. https://doi.org/10.1111/jcpt.13741
16. Stein AS, Schiller G, Benjamin R, et al. Neurologic adverse events in patients with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab: management and mitigating factors. *Ann Hematol.* 2019;98(1):159–167. https://doi.org/10.1007/s00277-018-3497-0
17. Bhojwani D, Bansal R, Wayne AS. Managing therapy-associated neurotoxicity in children with ALL. *Hematol Am Soc Hematol Educ Program.* 2021;2021(1):376–383. https://doi.org/10.1182/hematology.2021000269
18. Martinelli G, Boissel N, Chevallier P, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study. *J Clin Oncol.* 2017;35(16):1795–1802. https://doi.org/10.1200/JCO.2017.75.0489
19. Locatelli F, Zugmaier G, Rizzari C, et al. Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. *JAMA*. 2021;325(9):843–854. https://doi.org/10.1001/jama.2021.0987
20. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. *J Clin Invest.* 2016;126(6):2123–2138. https://doi.org/10.1172/JCI85309
21. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood.* 2019;133(24):2625. https://doi.org/10.1182/blood.2019001109 Blood. 2018;131(14):1522-1531.
22. Hedrick CC, Malanchi I. Neutrophils in cancer: heterogeneous and multifaceted. *Nat Rev Immunol.* 2022;22(3):173–187. https://doi.org/10.1038/s41577-021-00571-6
23. Liu S, Wu W, Du Y, et al. The evolution and heterogeneity of neutrophils in cancers: origins, subsets, functions, orchestrations and clinical applications. *Mol Cancer.* 2023;22(1):148. https://doi.org/10.1186/s12943-023-01843-6
24. Zugmaier G, Topp MS, Alekar S, et al. Long-term follow-up of serum immunoglobulin levels in blinatumomab-treated patients with minimal residual disease-positive B-precursor acute lymphoblastic leukemia. *Blood Cancer J.* 2014;4:244. https://doi.org/10.1038/bcj.2014.64
25. Lamble AJ, Kovach AE, Shah NN. How I treat postimmunotherapy relapsed B-ALL. *Blood.* 2026;145(1):64–74. https://doi.org/10.1182/blood.2024024517
26. Coorens T, Collord G, Treger TD, et al. Clonal origin of KMT2A wild-type lineage-switch leukemia following CAR-T cell and blinatumomab therapy. *Nat Cancer.* 2023;4(8):1095–1101. https://doi.org/10.1038/s43018-023-00604-0
27. Zhang AL, Yang LP, Hu X. Meta-analysis of CYP2C19 allele frequency in healthy Asian population. *Chin J Evid Based Med.* 2013;13(12):1431–1439. https://doi.org/10.7507/1672-2531.20130246
28. Kumar BV, Connors TJ, Farber DL. Human T Cell Development, Localization, and Function throughout Life. *Immunity.* 2018;48(2):202–213. https://doi.org/10.1016/j.immuni.2018.01.007
29. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. *J Clin Oncol.* 2016;34(36):4381–4389. https://doi.org/10.1200/JCO.2016.67.3301

30. Fullerton JL, Hay J, Bryant-Craig C, et al. Pediatric Traumatic Brain Injury and Microvascular Blood-Brain Barrier Pathology. *JAMA Netw Open.* 2024;7(11):e2446767. https://doi.org/10.1001/jamanetworkopen.2024.46767
31. Saravia J, Raynor JL, Chapman NM, et al. Signaling networks in immunometabolism. *Cell Res.* 2020;30(4):328–342. https://doi.org/10.1038/s41422-020-0301-1
32. Li H, Zhao W, Yang F, et al. Immunosenescence Inventory-a multi-omics database for immune aging research. *Nucleic Acids Res.* 2025;53(D1):D1047–D1054. https://doi.org/10.1093/nar/gkae1102
33. He ZX, Huang XQ, Chen DY, et al. A systematic review of pharmacoeconomic evaluation studies on National Reimbursement Drug List negotiated drugs in China. *Chin J Evid Based Med.* 2023;23(2):159–169. https://doi.org/10.7507/1672-2531.202207108
34. An YH, Jiang ZW, Zheng Y, et al. Data mining and analysis of adverse events associated with eculizumab based on FAERS. *Chin J Hosp Pharm.* 2024;44(9):1069–1074. https://doi.org/10.13286/j.1001-5213.2024.09.10
35. Shi YJ, Han Y, Wang Y, et al. Efficacy and adverse reactions of blinatumomab in 13 cases of relapsed/refractory acute lymphoblastic leukemia. *Chin J Hematol.* 2023;44(6):516–519. https://doi.org/10.3760/cma.j.issn.0253-2727.2023.06.015
36. Zhang F, Ding MM, Lu AD, et al. Blinatumomab for treatment of refractory/relapsed acute B-lymphoblastic leukemia in 2 children. *Chin J Appl Clin Pedia.* 2022;37(17):1341–1343. https://doi.org/10.3760/cma.j.cn101070-20210908-01096
37. Hu XJ, Zhang L, Xu YF, et al. CD19/CD3 bispecific antibody for treatment of pediatric B-ALL complicated with Trousseau syndrome: a case report and literature review. *Adv Clin Med.* 2023;13(8):13388–13395. https://doi.org/10.12677/ACM.2023.1381871
38. Shah M, Rahman A, Theoret MR, et al. The drug-dosing conundrum in oncology - when less is more. *N Engl J Med.* 2021;385(16):1445–1447. https://doi.org/10.1056/NEJMp2109826