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ORIGINAL RESEARCH

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Signal detection of adverse reactions for bendamustine based on FDA adverse event reporting system

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ABSTRACT

Background: This study aimed to analyze the adverse events to bendamustine using data obtained from the Food and Drug Administration open public data project (openFDA) and to provide a reference for its use in clinical practice.

Research design and methods: Adverse events (AEs) due to bendamustine usage reported from 1 January 2008 to 31 March 2023 were collected from the FDA Adverse Event Reporting System (FAERS). The reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian plausible propagation neural network (BCPNN), and multinomial gamma-Poisson distribution shrinking (MGPS) algorithms were used to identify signs of adverse reactions caused by bendamustine.

Results: A total of 4214 AE reports where bendamustine was considered as the first suspected drug were obtained from FAERS. The analysis revealed 214 AE risk signals, among which 141 met the criteria but they were not listed as possible side effects on the drug information sheet provided in the package.

Conclusion: Our findings identified numerous common AEs with previously reported clinical observations. We also identified some signs of potential new AEs, indicating the need of careful clinical monitoring of patients treated with bendamustine and further risk identification research about this drug.

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KEYWORDS
Bendamustine; adverse event; real world; disproportionality analysis; openFDA

1. Introduction

Bendamustine is a bifunctional nitrogen mustard derivative containing a purine-like benzimidazole ring, which may enhance its clinical efficacy [1]. The chemical structure of bendamustine comprises a nitrogen mustard moiety, benzimidazole ring, and n-butyric acid side chains. Bendamustine is active against both quiescent and dividing cells and exerts its antitumor effects through the alkylation of deoxyribonucleic acid (DNA), causing longitudinal and transverse crosslinking of single or double strands and interfering with further DNA synthesis and repair. Preclinical studies suggest that bendamustine can cause cell death through apoptosis and other pathways that disrupt normal cell division. Clinical trials have shown that bendamustine significantly reduces recurrence and mortality rates in cancer patients.

Bendamustine was approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic lymphocytic leukemia and inert B-cell non-Hodgkin's lymphoma that progressed after treatment with rituximab or a rituximab-containing regimen in March 2008 and October 2008, respectively. In December 2018, it was approved for marketing in China.

The FDA's open public data program, openFDA, was established in June 2014 that allowed the public to retrieve and access public data from FDA databases. In this paper, we retrieved the AE reports of bendamustine and its characteristics from the data obtained from openFDA, analyze the reports from multiple perspectives to provide reference for prescribing clinical medication, and promote the rational application of drugs. The management procedures for adverse drug reactions mainly include monitoring and identifying side effects. Relevant personnel such as healthcare providers and patients closely observe any potential adverse drug reactions, assess and categorize them, promptly report them through the adverse reaction reporting system, and take corresponding measures.

2. Methods

2.1. Data sources

The data were obtained from the Adverse Drug Events (ADR) database on the openFDA platform. Data were extracted using the Open-Vigil-FDA analysis tool, which directly extracts structured ADR information from the openFDA database using an application program interface (API) in an efficient and accurate manner. AEs were described using preferred terms (PT) included in the Medical Dictionary of Regulatory Activities Adverse Drug Event Thesaurus, and AEs were classified using the System Organ Classification (SOC). The reports recorded from January 2008 to March 2023 were analyzed.

2.2. Statistical analysis

Disproportionality analysis was performed by combining four algorithms: reporting odds ratio (ROR), proportional reporting

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ratio (PRR), Bayesian plausible propagation neural network (BCPNN), and MGPS methods. ROR and PRR have high sensitivity, whereas BCPNN and MGPS have satisfactory adverse drug reaction (ADR) prediction ability. These were used to quantify the signs of bendamustine-associated adverse events (AEs). The used calculation formulas, detection indices, and thresholds are shown in Table 1. Cases where AE criteria were met with at least one of the four algorithms were considered as positive drug-associated signals. In this study we selected AE signals that simultaneously met the criteria of the four algorithms to make the results more convincing.

3. Results

3.1. General characteristics

A total of 4214 AE reports for bendamustine were found from 1 January 2008 to 31 March 2023. The annual distribution, as shown in Figure 1, increased year by year from 2008 to 2012, reaching a peak in 2012 with a total of 1156 cases, and then gradually decreased and stabilized. The characteristics of bendamustine-associated AEs are shown in Table 2. Except for unspecified reported cases, the proportion of AE reports due to bendamustine was higher among males than among females (49.88% vs. 32.25%). In terms of age distribution, the highest number of reports were recorded for the elderly (aged >65 years; 35.86%; $n = 1511$), followed by adults (aged 18–65 years; 22.62%; $n = 953$), with a small number of reports being reported in minors. Bendamustine-associated adverse reactions were primarily reported from the United States, accounting for > 55% reports, followed by Japan (12.72%), Germany, France, and Italy. Overall, 2,340 reports of serious adverse reactions (including hospitalization, death, life-threatening, and disability) were found, accounting for 55.53% reports.

3.2. Adverse reaction risk signal analysis results

Figure 1 illustrates the annual distribution of adverse drug reactions to bendamustine, peaking in 2012 and gradually decreasing thereafter, stabilizing over time. With the increasing use of bendamustine, there might be an enhanced awareness of its potential adverse reactions, leading to proactive measures for their prevention. The details of 10 most common types of adverse reaction to bendamustine after removing logically implausible adverse reactions are listed in Table 3. Our analysis showed that the PTs for the top 10 AEs reported were fever, rash, neutropenia, febrile neutropenia, pancytopenia, malignant progression, infectious pneumonitis, thrombocytopenia, reduced platelet count, and anemia. SOC categorizes systemic

Table 1. Four main algorithms used to assess the potential association between bendamustine and AEs.

Algorithms	Equation	Criteria
ROR	ROR=ad/b/c	lower limit of 95% CI > 1, $N \geq 3$
PRR	PRR=a(c+d)/c/(a+b) χ^2=[(ad-bc)^2](a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]	PRR ≥2, χ^2 ≥4,$N \geq 3$
BCPNN	IC=$\log_2$a(a+b+c+d)/((a+c)(a+b)) 95%CI=E(IC)±2 V(IC)^0.5	IC025 > 0
MGPS	EBGM=a(a+b+c+d)/(a+c)/(a+b) 95%CI=$e^{\ln(EBGM)\pm1.96(1/a+1/b+1/c+1/d)^{0.5}}$	EBGM05 > 2

Notes: Equation: a, number of reports containing both the target drug and target adverse drug reactions; b, number of reports containing other adverse drug reactions to the target drug; c, number of reports containing the target adverse drug reactions to other drugs; d, number of reports containing both other drugs and other adverse drug reactions.
Abbreviations: 95% CI, 95% confidence interval; N, number of reports; χ^2,chi-squared; IC, information component; IC025, the lower limit of 95% IC; E(IC), the IC expectations; V(IC), the variance of IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

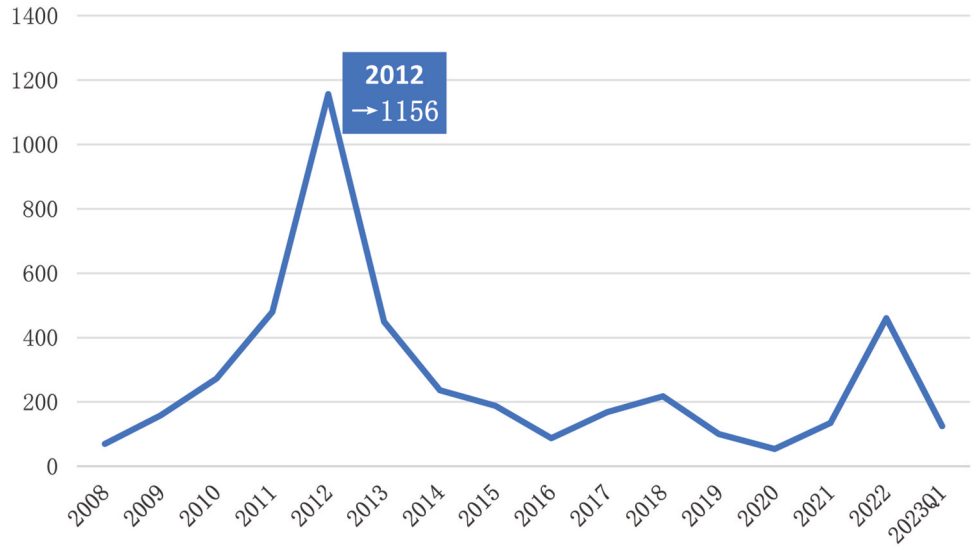

Figure 1. The annual distribution of bendamustine adverse reaction reports.

Table 2. Clinical characteristics of bendamustine use reported in the FAERS Database (January 2008 to March 2023).

Characteristics	Case Number, n	Case Proportion, %
Number of events	4214	
Gender		
Male	2102	49.88
Female	1359	32.25
Unknown	753	17.87
Age(years)		
<18	14	0.33
18–65	953	22.62
>65	1511	35.86
Unknown	1736	41.2
Reported countries (top five)		
United States (US)	2346	55.67
Japan (JP)	536	12.72
Germany (DE)	342	8.12
France (FR)	211	5.01
Italy(IT)	130	3.08
Serious outcome		
Hospitalization – initial or prolonged (HO)	1464	34.74
Death (DE)	603	14.31
Life-threatening (LT)	206	4.89
Disability (DS)	67	1.59

diseases and various reactions by the site of administration, skin and subcutaneous tissue diseases, blood and lymphatic system diseases, benign, malignant, and tumors of undetermined nature, respiratory, thoracic, and mediastinal disorders, and various investigations. The number of cases for these 10 AEs was 1,835, accounting for 43.55% adverse event reports.

ADR risk signal analysis was performed for the 4214 adverse reaction reports. A total of 214 adverse reaction risk signals were detected, among which 141 were not listed as AEs in the drug specification, involving 20 system organ classifications, with variations in each system organ (Table 4).The detailed results of the PTs of the AEs involved in the 214 risk signals are shown in Table 5.

4. Discussion

4.1. Analysis of ADR composition

The acquisition of the highest number of reports from the United States (55.67%) can be attributed to the fact that FDA database is a U.S.A.-based resource. The time of commercialization of bendamustine in different countries could also be considered as a dictating factor. One may assume similar guideline-based treatments in US and the reporting countries in CLL and NHL. The fact that Centres in Japan and Europe contribute to the database is a strength, making results more representative. ADR were mainly reported in patients aged >65 years, which may be related to the predominance of elderly patients. The high proportion of serious ADR events (including hospitalization, death, life-threatening, and disability) (55.83% of all reports) suggests that more attention should be paid while clinically using this drug, more related ADRs should be explored, and clinicians should increase alertness toward the occurrence of serious ADRs.

Table 3. Top 10 types of adverse reactions to bendamustine.

Preferred Terms (PTs)	PT/N	Case Proportion, %	SOC
Pyrexia	344	8.16	General disorders and administration site conditions
Rash	332	7.88	Skin and subcutaneous tissue disorders
Neutropenia	200	4.75	Blood and lymphatic system disorders
Febrile neutropenia	157	3.73	General disorders and administration site
Pancytopenia	152	3.61	Blood and lymphatic system disorders
Malignant neoplasm progression	141	3.35	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Pneumonia	140	3.32	Respiratory, thoracic and mediastinal disorders
Thrombocytopenia	130	3.08	Blood and lymphatic system disorders
Platelet count decreased	120	2.85	Investigations
Anaemia	119	2.82	Blood and lymphatic system disorders

Table 4. ADR events involving system organs.

SOC	PT/N	ROR (95%CI)	PRR (95%CI)	IC (IC025)	EBGM (EBGM05)
Blood and lymphatic system disorders	1164	11.34 (10.6–12.31)	8.48 (8.08–8.91)	3.08 (2.86)	8.46 (7.91)
General disorders and administration site conditions	976	10.47 (9.74–11.25)	8.28 (7.83–8.74)	3.04 (2.81)	8.25 (7.68)
Skin and subcutaneous tissue disorders	564	5.67 (5.19–6.19)	5.04 (4.67–5.45)	2.33 (2.04)	5.03 (4.61)
Infections and infestations	560	8.19 (7.49–8.95)	7.23 (6.69–7.81)	2.85 (2.55)	7.21 (6.6)
Investigations	559	10.25 (9.38–11.21)	9.02 (8.35–9.75)	3.17 (2.87)	8.99 (8.23)
Respiratory, thoracic and mediastinal disorders	357	4.53 (4.07–5.05)	4.24 (3.83–4.68)	2.08 (1.72)	4.23 (3.79)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	195	9.16 (7.93–10.58)	8.78 (7.66–10.08)	3.13 (2.65)	8.76 (7.58)
Immune system disorders	180	7.04 (6.07–8.18)	6.79 (5.88–7.83)	2.76 (2.26)	6.77 (5.83)
Metabolism and nutrition disorders	127	7.79 (6.53–9.3)	7.59 (6.39–9.01)	2.92 (2.33)	7.57 (6.34)
tissue disorders					
Vascular disorders	118	9.77 (8.13–11.74)	9.53 (7.97–11.38)	3.25 (2.64)	9.49 (7.9)
Neoplasms benign, malignant and	108	5.47 (4.52–6.63)	5.36 (4.45–6.46)	2.42 (1.79)	5.35 (4.42)
Congenital, familial and genetic disorders	90	4.93 (4–6.08)	4.85 (3.95–5.95)	2.27 (1.59)	4.84 (3.93)
Cardiac disorders	71	3.69 (2.91–4.66)	3.64 (2.89–4.59)	1.86 (1.09)	3.64 (2.88)
Injury, poisoning and procedural complications	68	14.52 (11.42–8.46)	14.3 (11.29–8.11)	3.83 (3.04)	14.22 (11.18)
Gastrointestinal disorders	40	8.01 (5.87–10.95)	7.95 (5.84–10.82)	2.99 (1.98)	7.92 (5.8)
Renal and urinary disorders	21	9.94 (6.47–15.27)	9.9 (6.45–15.17)	3.3 (1.95)	9.86 (6.42)
Hepatobiliary disorders	20	11.89 (7.65–18.47)	11.84 (7.64–18.35)	3.56 (2.17)	11.79 (7.59)
Social circumstances	13	11.73 (6.79–20.24)	11.69 (6.79–20.14)	3.54 (1.86)	11.64 (6.75)
Musculoskeletal and connective tissue disorders	8	26.23 (13.06–52.67)	26.18 (13.05–52.51)	4.7 (2.63)	25.92 (12.9)
Endocrine disorders	5	22.72 (11.47–66.95)	27.68 (11.47–66.8)	4.78 (2.3)	27.39 (11.34)

Table 5. Comparison of Signal Intensity Reported for Bendamustine at preferred term levels by SOC classification.

SOC	PTs	PT/N	ROR(95%CI)	PRR(95%CI)	IC(IC025)	EBGM (EBGM05)
Metabolism and nutrition disorders	tumour lysis syndrome	56	40.7 (31.2–53.09)	40.17 (30.9–52.22)	5.31 (4.44)	39.55(30.32)
	respiratory failure	39	3.27 (2.39–4.48)	3.25 (2.38–4.44)	1.7 (0.68)	3.25 (2.37)
	hypercalcaemia*	12	6.53 (3.7–11.52)	6.51 (3.7–11.47)	2.7 (0.97)	6.5 (3.69)
	hyperuricaemia*	8	14.33 (7.15–28.74)	14.31 (7.15–28.65)	3.83 (1.78)	14.23 (7.1)
	hypernatraemia*	7	9.52 (4.53–20.02)	9.51 (4.53–19.96)	3.24 (1.08)	9.48 (4.51)
	nephrogenic diabetes insipidus*	5	23.97 (9.93–57.86)	23.94 (9.93–57.74)	4.57 (2.1)	23.72 (9.83)
Hepatobiliary disorders	hepatitis b	15	13.61 (8.19–22.63)	13.56 (8.17–22.51)	3.75 (2.18)	13.5 (8.12)
	hepatitis b reactivation	3	8.57 (3.56–20.64)	8.56 (3.56–20.6)	3.09 (0.64)	8.54 (3.55)
Infections and infestations	sepsis	89	5.17 (4.19–6.38)	5.08 (4.14–6.24)	2.34 (1.65)	5.07 (4.11)
	cytomegalovirus infection	75	30.32 (24.1–38.15)	29.8 (23.78–37.34)	4.88 (4.13)	29.46 (23.41)
	infection	71	3.03 (2.4–3.83)	2.99 (2.38–3.77)	1.58 (0.81)	2.99 (2.37)
	herpes zoster	49	5.19 (3.91–6.88)	5.14 (3.89–6.79)	2.36 (1.44)	5.13 (3.87)
	cytomegalovirus viremia	37	74 (53.29–102.77)	73.36 (52.98–101.59)	6.16 (5.09)	71.29 (51.33)
	cytomegalovirus chorioretinitis*	22	79.04 (51.65–120.96)	78.63 (51.49–120.08)	6.25 (4.9)	76.25 (49.82)
	viral infection	19	3.83 (2.44–6.01)	3.82 (2.44–5.98)	1.93 (0.51)	3.81 (2.43)
	aspergillus infection*	13	10.43 (6.04–17.99)	10.4 (6.04–17.91)	3.37 (1.7)	10.36 (6)
	bacterial infection*	13	4.92 (2.85–8.48)	4.91 (2.85–8.45)	2.29 (0.62)	4.9 (2.84)
	bronchopulmonary aspergillosis*	13	11.3 (6.55–19.5)	11.27 (6.54–19.41)	3.49 (1.81)	11.22 (6.5)
	cytomegalovirus infection reactivation	11	32.8 (18.08–59.5)	32.72 (18.06–59.26)	5.01 (3.2)	32.3 (17.81)
	pneumonia cytomegaloviral	11	45.29 (24.93–82.28)	45.17 (24.9–81.95)	5.47 (3.66)	44.38 (24.43)
	device related infection*	11	4.59 (2.54–8.3)	4.58 (2.54–8.26)	2.19 (0.4)	4.57 (2.53)
	pneumonia fungal*	10	14.28 (7.66–26.6)	14.25 (7.66–26.51)	3.82 (1.95)	14.17 (7.61)
	cytomegalovirus enterocolitis*	9	89.49 (45.99–174.12)	89.3 (45.96–173.52)	6.43 (4.43)	86.23 (44.32)
	bacteraemia	9	5.37 (2.79–10.34)	5.36 (2.79–10.31)	2.42 (0.47)	5.35 (2.78)
	oral candidiasis	8	4.59 (2.29–9.2)	4.59 (2.29–9.17)	2.2 (0.15)	4.58 (2.29)
	pneumonia bacteria*	8	6.48 (3.24–12.99)	6.47 (3.24–12.95)	2.69 (0.64)	6.46 (3.23)
	clostridial infection*	7	9.79 (4.66–20.57)	9.77 (4.65–20.51)	3.28 (1.12)	9.74 (4.63)
	pneumocystis jirovecii infection	7	38.39 (18.19–81.04)	38.33 (18.18–80.81)	5.24 (3.06)	37.76 (17.89)
	neutropenic infection	7	49.13 (23.24–103.87)	49.05 (23.23–103.58)	5.59 (3.4)	48.12 (22.76)
	bacterial sepsis*	6	13.9 (6.23–31.03)	13.88 (6.23–30.95)	3.79 (1.49)	13.81 (6.19)
	escherichia sepsis*	5	12.34 (5.12–29.73)	12.33 (5.12–29.67)	3.62 (1.16)	12.27 (5.09)
	pseudomembranous colitis*	5	13.77 (5.71–33.17)	13.75 (5.71–33.1)	3.77 (1.31)	13.68 (5.68)
	cytomegalovirus colitis*	5	16.6 (6.88–40.02)	16.58 (6.88–39.93)	4.04 (1.58)	16.48 (6.83)
	retinitis*	5	37.4 (15.46–90.5)	37.36 (15.45–90.3)	5.2 (2.72)	36.82 (15.22)
	jc virus infection*	4	18.36 (6.86–49.11)	18.34 (6.86–49.02)	4.19 (1.52)	18.21 (6.81)
	opportunistic infection	4	11.3 (4.23–30.18)	11.29 (4.23–30.13)	3.49 (0.83)	11.24 (4.21)
	listeria sepsis*	4	112.86 (41.42–307.54)	112.75 (41.41–306.97)	6.75 (4.01)	107.89 (39.59)
	acarodermatitis*	4	21.92 (8.19–58.69)	21.9 (8.19–58.58)	4.44 (1.77)	21.72 (8.11)
	systemic infection	4	10.88 (4.07–29.06)	10.87 (4.07–29.01)	3.44 (0.78)	10.82 (4.05)
	disseminated varicella zoster virus infection*	3	18.25 (5.86–56.85)	18.24 (5.86–56.76)	4.18 (1.25)	18.11 (5.82)
	enterocolitis infectious*	3	19.05 (6.11–59.33)	19.03 (6.11–59.24)	4.24 (1.31)	18.89 (6.07)
	meningoencephalitis herpetic*	3	20.63 (6.62–64.28)	20.61 (6.62–64.19)	4.35 (1.42)	20.45 (6.56)
	cryptococcosis*	3	10.79 (3.47–33.56)	10.79 (3.47–33.51)	3.43 (0.5)	10.74 (3.45)
	device related sepsis*	3	9.79 (3.15–30.42)	9.78 (3.15–30.38)	3.28 (0.37)	9.74 (3.13)

(*Continued*)

Table 5. (Continued).

SOC	PTs	PT/N	ROR(95%CI)	PRR(95%CI)	IC(IC025)	EBGM (EBGM05)
Investigations	platelet count decreased	120	7.1 (5.92–8.51)	6.92 (5.8–8.26)	2.79 (2.19)	6.91 (5.76)
	white blood cell count decreased	114	6.4 (5.32–7.72)	6.26 (5.22–7.5)	2.64 (2.03)	6.24 (5.18)
	neutrophil count decreased	106	17.38 (14.32–21.09)	16.97 (14.05–20.49)	4.08 (3.44)	16.86 (13.89)
	lymphocyte count decreased	81	28.05 (22.49–34.99)	27.53 (22.16–34.2)	4.77 (4.04)	27.24 (21.84)
	blood lactate dehydrogenase increased*	27	13.66 (9.35–19.97)	13.58 (9.32–19.8)	3.76 (2.54)	13.51 (9.25)
	c-reactive protein increased*	22	4.76 (3.13–7.24)	4.74 (3.13–7.2)	2.24 (0.92)	4.74 (3.11)
	blood bilirubin increased	17	4.12 (2.56–6.64)	4.11 (2.56–6.61)	2.04 (0.55)	4.1 (2.55)
	cytomegalovirus test positive	11	40.83 (22.48–74.14)	40.73 (22.46–73.84)	5.32 (3.51)	40.08 (22.07)
	ejection fraction decreased*	10	3.75 (2.01–6.97)	3.74 (2.01–6.95)	1.9 (0.03)	3.74 (2.01)
	cd4 lymphocytes decreased	8	23.78 (11.85–47.74)	23.74 (11.84–47.59)	4.56 (2.5)	23.52 (11.72)
	troponin increased*	7	6.85 (3.26–14.39)	6.84 (3.26–14.35)	2.77 (0.61)	6.82 (3.25)
	blood uric acid increased*	6	7.51 (3.37–16.75)	7.5 (3.37–16.71)	2.9 (0.61)	7.48 (3.36)
	klebsiella test positive*	5	51.95 (21.42–126.03)	51.89 (21.41–125.75)	5.67 (3.18)	50.85 (20.96)
	granulocyte count decreased	5	25.76 (10.67–62.21)	25.73 (10.67–62.07)	4.67 (2.2)	25.48 (10.55)
	blood culture positive*	5	12.99 (5.39–31.29)	12.97 (5.39–31.22)	3.69 (1.23)	12.91 (5.36)
	t-lymphocyte count decreased	3	26.5 (8.49–82.7)	26.48 (8.49–82.57)	4.71 (1.78)	26.21 (8.4)
	aspiration bone marrow abnormal*	3	140.5 (43.89–449.81)	140.41 (43.89–449.14)	7.05 (4.01)	132.94 (41.53)
	biopsy bone marrow abnormal*	3	41.6 (13.29–130.27)	41.57 (13.29–130.07)	5.35 (2.4)	40.9 (13.06)
	bacterial test positive*	3	8.51 (2.74–26.45)	8.51 (2.74–26.41)	3.08 (0.17)	8.48 (2.73)
	neutrophil percentage increased*	3	26.41 (8.46–82.4)	26.39 (8.46–82.28)	4.71 (1.77)	26.12 (8.37)
Nervous system disorders	neuropathy peripheral*	51	3.21 (2.43–4.23)	3.18 (2.42–4.18)	1.67 (0.77)	3.18 (2.41)
	progressive multifocal leukoencephalopathy*	31	21.8 (15.29–31.08)	21.64 (15.22–30.78)	4.42 (3.28)	21.46 (15.05)
	polyneuropathy*	10	5.85 (3.14–10.88)	5.84 (3.14–10.84)	2.54 (0.67)	5.82 (3.13)
	guillain-barre syndrome*	8	11.88 (5.92–23.8)	11.85 (5.92–23.73)	3.56 (1.51)	11.8 (5.89)
	cerebral toxoplasmosis*	5	33.65 (13.92–81.37)	33.61 (13.91–81.19)	5.05 (2.58)	33.18 (13.72)
	demyelinating polyneuropathy*	3	19.75 (6.34–61.55)	19.74 (6.34–61.45)	4.29 (1.36)	19.59 (6.29)
Injury, poisoning and procedural complications	phlebitis	40	52.96 (38.67–72.55)	52.47 (38.42–71.66)	5.68 (4.66)	51.4 (37.53)
	prescribed underdose*	25	6.55 (4.42–9.72)	6.52 (4.41–9.64)	2.7 (1.45)	6.51 (4.39)
	subcutaneous emphysema*	3	18.8 (6.04–58.58)	18.79 (6.04–58.49)	4.22 (1.29)	18.66 (5.99)
Musculoskeletal and connective tissue disorders	chills	90	4.93 (4–6.08)	4.85 (3.95–5.95)	2.27 (1.59)	4.84 (3.93)
Congenital, familial and genetic disorders	aplasia*	8	26.23 (13.06–52.67)	26.18 (13.05–52.51)	4.7 (2.63)	25.92 (12.9)
Respiratory, thoracic and mediastinal disorders	pneumonia	140	2.66 (2.25–3.15)	2.61 (2.22–3.07)	1.38 (0.82)	2.61 (2.2)
	pleural effusion*	45	4.75 (3.54–6.37)	4.71 (3.52–6.3)	2.23 (1.28)	4.7 (3.5)
	pneumocystis jirovecii pneumonia	38	19.86 (14.41–27.37)	19.69 (14.33–27.06)	4.29 (3.25)	19.54 (14.18)
	pneumonitis	25	6.36 (4.29–9.43)	6.33 (4.28–9.36)	2.66 (1.41)	6.32 (4.26)
	hypoxia*	22	4.31 (2.83–6.55)	4.29 (2.83–6.51)	2.1 (0.77)	4.29 (2.82)
	coronavirus infection*	21	15.28 (9.94–23.49)	15.21 (9.91–23.33)	3.92 (2.56)	15.12 (9.84)
	lung infiltration*	11	8.8 (4.86–15.91)	8.78 (4.86–15.85)	3.13 (1.33)	8.75 (4.84)
	pneumothorax*	11	4.1 (2.27–7.4)	4.09 (2.26–7.38)	2.03 (0.23)	4.08 (2.26)
	obliterative bronchiolitis*	7	33.7 (15.98–71.1)	33.65 (15.97–70.9)	5.05 (2.87)	33.21 (15.74)
	atelectasis*	7	5.65 (2.69–11.88)	5.65 (2.69–11.85)	2.49 (0.33)	5.64 (2.68)
	pulmonary toxicity	6	5.05 (2.27–11.26)	5.04 (2.27–11.23)	2.33 (0.04)	5.04 (2.26)
	organising pneumonia	6	7.18 (3.22–16.02)	7.18 (3.22–15.98)	2.84 (0.54)	7.16 (3.21)
	atypical pneumonia	5	9.78 (4.06–23.56)	9.77 (4.06–23.51)	3.28 (0.82)	9.74 (4.04)
	pneumonia pseudomonal*	4	15.16 (5.67–40.54)	15.15 (5.67–40.46)	3.91 (1.25)	15.06 (5.63)
	pneumonia pneumococcal*	3	14.72 (4.73–45.8)	14.71 (4.73–45.74)	3.87 (0.95)	14.63 (4.7)
	diffuse alveolar damage	3	16.66 (5.35–51.87)	16.65 (5.35–51.79)	4.05 (1.12)	16.54 (5.31)
	pneumothorax spontaneous*	3	26.41 (8.46–82.4)	26.39 (8.46–82.28)	4.71 (1.77)	26.12 (8.37)

(*Continued*)

Table 5. (Continued).

SOC	PTs	PT/N	ROR(95%CI)	PRR(95%CI)	IC(IC025)	EBGM (EBGM05)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	malignant neoplasm progression*	141	8.28 (7–9.8)	8.04 (6.83–9.46)	3 (2.45)	8.02 (6.78)
	squamous cell carcinoma*	21	13.04 (8.49–20.05)	12.98 (8.47–19.92)	3.69 (2.33)	12.92 (8.41)
	basal cell carcinoma*	16	6.79 (4.15–11.1)	6.76 (4.15–11.04)	2.75 (1.22)	6.75 (4.13)
	tumour flare*	8	74.46 (36.83–150.54)	74.32 (36.81–150.06)	6.17 (4.09)	72.19 (35.71)
	bowen's disease*	3	13.69 (4.4–42.59)	13.68 (4.4–42.53)	3.77 (0.84)	13.61 (4.37)
	malignant pleural effusion*	3	12.21 (3.92–37.97)	12.2 (3.93–37.91)	3.6 (0.68)	12.14 (3.9)
	keratoacanthoma*	3	28.42 (9.1–88.73)	28.4 (9.11–88.6)	4.81 (1.87)	28.09 (9)
Immune system disorders	vasculitis*	31	17.53 (12.3–24.98)	17.41 (12.24–24.75)	4.11 (2.97)	17.29 (12.13)
	hypogammaglobulinaemia*	29	35.09 (24.29–50.68)	34.85 (24.19–50.22)	5.1 (3.93)	34.38 (23.8)
	infusion related reaction	29	4.59 (3.18–6.61)	4.56 (3.17–6.56)	2.19 (1.02)	4.56 (3.16)
	interstitial lung disease	28	3.7 (2.55–5.37)	3.68 (2.54–5.33)	1.88 (0.69)	3.68 (2.54)
	drug eruption*	12	4.51 (2.56–7.95)	4.5 (2.56–7.92)	2.17 (0.43)	4.49 (2.55)
	immunosuppression*	11	8.75 (4.84–15.84)	8.73 (4.84–15.78)	3.12 (1.32)	8.71 (4.81)
	toxic epidermal necrolysis	10	3.93 (2.11–7.31)	3.92 (2.11–7.29)	1.97 (0.1)	3.92 (2.11)
	immune thrombocytopenia*	9	5.9 (3.06–11.36)	5.89 (3.06–11.32)	2.56 (0.6)	5.88 (3.05)
	humoral immune defect	9	338.97 (168.82–680.64)	338.25 (168.68–678.3)	8.22 (6.11)	297.78 (148.3)
	toxic skin eruption*	8	5.69 (2.84–11.39)	5.68 (2.84–11.36)	2.5 (0.45)	5.67 (2.83)
	dermatitis exfoliative generalised*	4	7.82 (2.93–20.88)	7.81 (2.93–20.84)	2.96 (0.3)	7.79 (2.92)
Endocrine disorders	neuroendocrine carcinoma of the skin*	5	27.72 (11.47–66.95)	27.68 (11.47–66.8)	4.78 (2.3)	27.39 (11.34)
Skin and subcutaneous tissue disorders	rash	332	4.56 (4.08–5.1)	4.28 (3.86–4.75)	2.1 (1.72)	4.28 (3.82)
	stevens-johnson syndrome	47	12.83 (9.62–17.12)	12.7 (9.55–16.89)	3.66 (2.72)	12.64 (9.47)
	rash maculo-papular*	37	11.39 (8.23–15.75)	11.3 (8.19–15.58)	3.49 (2.44)	11.25 (8.13)
	rash erythematous*	30	4.85 (3.39–6.95)	4.82 (3.38–6.89)	2.27 (1.12)	4.82 (3.36)
	rash pruritic*	27	3.25 (2.23–4.75)	3.24 (2.22–4.72)	1.69 (0.49)	3.24 (2.22)
	rash macular*	19	4.09 (2.6–6.42)	4.07 (2.6–6.38)	2.02 (0.61)	4.07 (2.59)
	skin reaction	19	7.86 (5–12.34)	7.82 (4.99–12.26)	2.96 (1.55)	7.8 (4.97)
	infusion site erythema*	17	17.81 (11.04–28.72)	17.74 (11.02–28.56)	4.14 (2.65)	17.62 (10.93)
	rash papular*	11	3.95 (2.18–7.14)	3.94 (2.18–7.11)	1.98 (0.18)	3.94 (2.18)
	skin toxicity	7	7.86 (3.74–16.51)	7.85 (3.74–16.47)	2.97 (0.8)	7.82 (3.72)
	rash morbilliform*	5	11.13 (4.62–26.82)	11.12 (4.62–26.76)	3.47 (1.01)	11.08 (4.6)
	infusion site discolouration*	5	49.27 (20.32–119.47)	49.22 (20.32–119.21)	5.59 (3.1)	48.28 (19.91)
	acute febrile neutrophilic dermatosis*	4	9.24 (3.46–24.67)	9.23 (3.46–24.63)	3.2 (0.54)	9.2 (3.44)
	infusion site vesicles*	4	63.66 (23.59–171.84)	63.6 (23.59–171.52)	5.96 (3.25)	62.04 (22.98)

(*Continued*)

Table 5. (Continued).

SOC	PTs	PT/N	ROR(95%CI)	PRR(95%CI)	IC(IC025)	EBGM (EBGM05)
General disorders and administration site conditions	pyrexia	344	6.95 (6.22–7.76)	6.46 (5.84–7.15)	2.69 (2.32)	6.45 (5.78)
	febrile neutropenia	157	17.82 (15.19–20.91)	17.2 (14.74–20.06)	4.09 (3.56)	17.08 (14.56)
	disease progression*	87	3.95 (3.19–4.88)	3.89 (3.16–4.79)	1.96 (1.26)	3.88 (3.14)
	extravasation	71	109.34 (86.05–138.94)	107.52 (84.94–136.09)	6.69 (5.9)	103.09 (81.13)
	infusion site extravasation*	55	62.17 (47.49–81.38)	61.37 (47.05–80.06)	5.9 (5.03)	59.91 (45.77)
	general physical health deterioration	52	3.04 (2.31–4)	3.01 (2.3–3.95)	1.59 (0.7)	3.01 (2.29)
	infusion site pain	43	27.98 (20.68–37.85)	27.7 (20.54–37.36)	4.78 (3.8)	27.41 (20.26)
	infusion site irritation	23	167.73 (109.84–256.12)	166.82 (109.48–254.18)	7.29 (5.94)	156.37 (102.4)
	infusion site swelling	22	28.69 (18.82–43.72)	28.54 (18.77–43.4)	4.82 (3.48)	28.23 (18.52)
	infusion site reaction	19	68.21 (43.2–107.71)	67.91 (43.1–107.01)	6.05 (4.61)	66.13 (41.88)
	mucosal inflammation*	19	4.87 (3.1–7.65)	4.86 (3.1–7.61)	2.28 (0.86)	4.85 (3.09)
	febrile bone marrow aplasia*	11	27.94 (15.41–50.66)	27.87 (15.4–50.46)	4.79 (2.98)	27.57 (15.21)
	therapy partial responder*	11	6.32 (3.5–11.43)	6.31 (3.49–11.39)	2.65 (0.86)	6.29 (3.48)
	hyperthermia	10	8.2 (4.4–15.26)	8.18 (4.4–15.21)	3.03 (1.16)	8.16 (4.38)
	injection site phlebitis	10	292.52 (151.8–563.67)	291.82 (151.65–561.55)	8.03 (6.03)	261.21 (135.56)
	generalised oedema*	9	5.04 (2.62–9.69)	5.03 (2.62–9.66)	2.33 (0.37)	5.02 (2.61)
	infusion site induration*	9	60.96 (31.44–118.17)	60.83 (31.42–117.76)	5.89 (3.91)	59.4 (30.64)
	performance status decreased*	5	6.81 (2.83–16.39)	6.8 (2.83–16.36)	2.76 (0.31)	6.79 (2.82)
	systemic inflammatory response syndrome	4	6.59 (2.47–17.6)	6.59 (2.47–17.57)	2.72 (0.06)	6.57 (2.46)
	febrile infection*	3	20.51 (6.58–63.93)	20.5 (6.58–63.83)	4.35 (1.42)	20.34 (6.53)
	dysplasia*	3	15.04 (4.83–46.82)	15.03 (4.83–46.75)	3.9 (0.98)	14.95 (4.8)
	capillary leak syndrome*	3	10.44 (3.36–32.47)	10.44 (3.36–32.43)	3.38 (0.46)	10.4 (3.34)
	infusion site warmth*	3	20.74 (6.66–64.64)	20.73 (6.66–64.55)	4.36 (1.43)	20.56 (6.6)
	injection site oedema*	3	10.44 (3.36–32.47)	10.44 (3.36–32.43)	3.38 (0.46)	10.4 (3.34)
Social circumstances	refusal of treatment by patient*	10	9.65 (5.18–17.97)	9.63 (5.18–17.9)	3.26 (1.39)	9.6 (5.15)
	blood product transfusion dependent*	3	40.92 (13.07–128.1)	40.89 (13.07–127.91)	5.33 (2.38)	40.24 (12.85)
Renal and urinary disorders	urosepsis*	10	7.12 (3.82–13.25)	7.1 (3.82–13.2)	2.82 (0.95)	7.08 (3.81)
	cystitis haemorrhagic*	7	12.79 (6.08–26.89)	12.77 (6.08–26.82)	3.67 (1.5)	12.71 (6.04)
	stress urinary incontinence*	4	24.16 (9.02–64.72)	24.14 (9.02–64.6)	4.58 (1.91)	23.92 (8.93)
Gastrointestinal disorders	ileus*	15	8.3 (4.99–13.79)	8.27 (4.99–13.72)	3.04 (1.47)	8.25 (4.96)
	colitis ischaemic*	7	20.1 (7.51–53.8)	20.09 (7.51–53.7)	4.32 (1.65)	19.93 (7.45)
	enterocolitis*	6	6.37 (3.03–13.39)	6.36 (3.03–13.35)	2.67 (0.5)	6.35 (3.02)
	gastrointestinal toxicity	5	6.66 (2.77–16.03)	6.65 (2.77–16)	2.73 (0.27)	6.64 (2.76)
	intestinal pseudo-obstruction*	4	6.82 (3.06–15.2)	6.81 (3.06–15.17)	2.76 (0.47)	6.8 (3.05)
	neutropenic colitis*	3	10.43 (3.35–32.43)	10.42 (3.35–32.38)	3.38 (0.46)	10.38 (3.34)
Cardiac disorders	atrial fibrillation	48	2.99 (2.25–3.97)	2.97 (2.24–3.93)	1.57 (0.64)	2.96 (2.23)
	atrial flutter*	8	6.24 (3.11–12.49)	6.22 (3.11–12.45)	2.63 (0.58)	6.21 (3.1)
	left ventricular dysfunction*	6	5.35 (2.4–11.93)	5.35 (2.4–11.9)	2.42 (0.12)	5.34 (2.39)
	aortic valve incompetence*	5	9.48 (3.94–22.84)	9.47 (3.94–22.79)	3.24 (0.78)	9.44 (3.92)
	tachyarrhythmia*	4	10.4 (3.89–27.78)	10.39 (3.89–27.73)	3.37 (0.71)	10.35 (3.87)
Vascular disorders	septic shock	36	5.81 (4.18–8.06)	5.76 (4.16–7.98)	2.52 (1.47)	5.75 (4.14)
	infusion site phlebitis	15	565.76 (322.7–991.9)	563.75 (322.08–986.77)	8.84 (7.1)	459.54 (262.11)
	disseminated intravascular coagulation*	13	6.12 (3.55–10.55)	6.1 (3.54–10.51)	2.61 (0.93)	6.09 (3.53)
	vein disorder	12	14.49 (8.21–25.59)	14.46 (8.2–25.48)	3.85 (2.11)	14.38 (8.15)
	venoocclusive liver disease*	10	12.62 (6.78–23.52)	12.6 (6.77–23.43)	3.65 (1.77)	12.54 (6.73)
	thrombophlebitis*	8	15.16 (7.56–30.41)	15.14 (7.56–30.31)	3.91 (1.86)	15.05 (7.51)
	angiopathy	6	6.77 (3.04–15.1)	6.76 (3.04–15.06)	2.75 (0.46)	6.75 (3.03)
	aortic stenosis*	6	10.71 (4.8–23.89)	10.69 (4.8–23.83)	3.41 (1.11)	10.65 (4.77)
	vein discolouration*	3	40.69 (13–127.39)	40.66 (13–127.2)	5.32 (2.37)	40.02 (12.78)
	infusion site haematoma*	3	32.24 (10.32–100.73)	32.21 (10.32–100.58)	4.99 (2.05)	31.81 (10.18)
	vascular pain*	3	17.77 (5.71–55.35)	17.76 (5.71–55.27)	4.14 (1.21)	17.64 (5.66)
	injection site thrombosis*	3	61.04 (19.41–191.97)	61 (19.41–191.68)	5.9 (2.92)	59.56 (18.94)

(*Continued*)

Table 5. (Continued).

SOC	PTs	PT/N	ROR(95%CI)	PRR(95%CI)	IC(IC025)	EBGM (EBGM05)
Blood and lymphatic system disorders	neutropenia	200	9.17 (7.96–10.57)	8.78 (7.67–10.06)	3.13 (2.66)	8.76 (7.6)
	pancytopenia	152	18.72 (15.91–22.02)	18.08 (15.46–21.15)	4.17 (3.63)	17.96 (15.26)
	thrombocytopenia	130	7.69 (6.46–9.16)	7.49 (6.32–8.87)	2.9 (2.32)	7.47 (6.27)
	anaemia	119	4.08 (3.4–4.9)	4 (3.35–4.77)	2 (1.39)	3.99 (3.33)
	bone marrow failure*	55	14.04 (10.75–18.33)	13.87 (10.66–18.04)	3.79 (2.92)	13.79 (10.56)
	plasma cell myeloma*	44	5 (3.71–6.73)	4.95 (3.69–6.65)	2.31 (1.34)	4.95 (3.67)
	chronic lymphocytic leukaemia*	41	51.88 (38.03–70.79)	51.39 (37.78–69.91)	5.65 (4.65)	50.37 (36.91)
	haemolytic anaemia*	39	27.16 (19.78–37.29)	26.92 (19.66–36.85)	4.74 (3.71)	26.64 (19.4)
	leukopenia	36	4.74 (3.41–6.58)	4.71 (3.4–6.52)	2.23 (1.17)	4.7 (3.39)
	lymphopenia	33	14.65 (10.39–20.66)	14.55 (10.35–20.46)	3.85 (2.75)	14.47 (10.26)
	lymphadenopathy*	30	5.49 (3.84–7.87)	5.46 (3.82–7.81)	2.45 (1.29)	5.45 (3.81)
	autoimmune hemolytic anaemia*	28	41.24 (28.36–59.99)	40.98 (28.24–59.45)	5.33 (4.13)	40.33 (27.72)
	myelodysplastic syndrome	21	8.18 (5.32–12.56)	8.14 (5.31–12.48)	3.02 (1.66)	8.12 (5.28)
	aplasia pure red cell*	20	38.1 (24.48–59.32)	37.93 (24.41–58.92)	5.22 (3.83)	37.37 (24.01)
	acute myeloid leukemia	20	7.18 (4.62–11.14)	7.15 (4.61–11.07)	2.83 (1.45)	7.13 (4.59)
	haematotoxicity	20	13.21 (8.5–20.52)	13.15 (8.48–20.38)	3.71 (2.32)	13.08 (8.42)
	non-hodgkin's lymphoma*	17	16.36 (10.14–26.38)	16.29 (10.12–26.23)	4.02 (2.52)	16.19 (10.04)
	cytopenia	17	9.05 (5.61–14.58)	9.01 (5.6–14.5)	3.17 (1.68)	8.99 (5.58)
	lymphoma*	16	5.14 (3.14–8.4)	5.12 (3.14–8.35)	2.35 (0.82)	5.11 (3.13)
	mantle cell lymphoma*	13	58.17 (33.54–100.91)	58 (33.49–100.43)	5.83 (4.13)	56.7 (32.69)
	agranulocytosis*	12	4.63 (2.63–8.17)	4.62 (2.63–8.13)	2.21 (0.47)	4.61 (2.62)
	b-cell lymphoma*	11	18.31 (10.11–33.16)	18.26 (10.1–33.02)	4.18 (2.38)	18.14 (10.01)
	splenomegaly*	10	5.21 (2.8–9.69)	5.2 (2.8–9.66)	2.37 (0.5)	5.19 (2.79)
	eosinophilia	10	3.86 (2.08–7.19)	3.86 (2.08–7.16)	1.95 (0.07)	3.85 (2.07)
	haemophagocytic lymphohistiocytosis*	10	6.59 (3.54–12.27)	6.58 (3.54–12.23)	2.71 (0.84)	6.56 (3.53)
	neutropenic sepsis*	9	7.36 (3.82–14.17)	7.35 (3.82–14.12)	2.87 (0.92)	7.33 (3.81)
	diffuse large b-cell lymphoma*	7	7.51 (3.57–15.78)	7.5 (3.57–15.73)	2.9 (0.74)	7.48 (3.56)
	aplastic anemia *	7	8.62 (4.1–18.11)	8.6 (4.1–18.06)	3.1 (0.94)	8.58 (4.08)
	chronic lymphocytic leukemia recurrent *	6	47.16 (21.02–105.84)	47.1 (21.01–105.57)	5.53 (3.21)	46.24 (20.61)
	haemolysis	6	5.32 (2.39–11.85)	5.31 (2.39–11.83)	2.41 (0.11)	5.3 (2.38)
	mantle cell lymphoma recurrent *	4	75.24 (27.81–203.54)	75.17 (27.81–203.16)	6.19 (3.47)	72.99 (26.98)
	non-hodgkin's lymphoma recurrent *	4	55.48 (20.59–149.52)	55.43 (20.59–149.24)	5.76 (3.06)	54.24 (20.13)
	langerhans' cell histiocytosis *	4	53.97 (20.03–145.41)	53.92 (20.03–145.14)	5.72 (3.02)	52.8 (19.6)
	waldenstrom's macroglobulinaemia *	4	42.26 (15.72–113.59)	42.22 (15.72–113.38)	5.38 (2.69)	41.53 (15.45)
	diffuse large b-cell lymphoma recurrent *	3	13.23 (4.25–41.15)	13.22 (4.25–41.09)	3.72 (0.79)	13.15 (4.23)
	splenic marginal zone lymphoma recurrent *	3	1241.14 (310.3–4964.37)	1240.25 (310.28–4957.57)	9.69 (6.02)	827.17 (206.8)
	blastic plasmacytoid dendritic cell neoplasia *	3	232.71 (71.23–760.25)	232.55 (71.24–759.13)	7.73 (4.6)	212.7 (65.11)

*Indicates an adverse event not mentioned in the benzydamustine specificatio.

4.2. Analysis of screened ADR signals

Based on a disproportionality analysis, this study found that ADRs to bendamustine primarily occurred in patients with blood and lymphocyte disorders, skin and subcutaneous tissue disorders, systemic disorders, infections, and reactions at the site of administration. The ROR, PRR, and EBGM05 were > 70.0 for ADRs including but not limited to infusion site phlebitis, humoral immunodeficiency, injection site phlebitis, infusion site irritation, *Listeria* sepsis, extravasation, cytomegalovirus small intestinal colitis, cytomegalovirus choroidal retinitis, and cytomegalovirus-associated viremia. The distribution of adverse reactions, mostly consistent with the indications, indicates a certain representativeness of the clinical studies, revealing the most significant as well as new severe adverse reactions.

Bendamustine is a bifunctional mescaline-alkylating agent that is used to treat patients with hematologic malignancies. We found that hematologic AEs [2,3] such as neutropenia, decreased lymphocyte count [4], pancytopenia, thrombocytopenia, and anemia frequently occurred after bendamustine administration. In patients with prolonged myelosuppression, delayed dosing is required [5,6]. This myelosuppressive and cytotoxic drug reduces the number of $CD4^+$ lymphocytes [7] and the CD4/CD8 ratio, causing dose-dependent immunosuppression. This increases the risk of infection-related complications in patients. Previous research has demonstrated the need for careful monitoring of lymphocyte counts during clinical treatment with bendamustine [8,9]. A meta-analysis that presented data on the AEs associated with bendamustine-containing regimens revealed infections as the most common AE, followed by neutropenia and lymphocytopenia. This study, based on data obtained from openFDA, identified the signs of blood and lymphocyte ADRs and diseases that developed due to bendamustine administration with significant signal intensity. These signs included pancytopenia, lymphopenia, hemolysis, myelodysplastic syndromes, and acute myeloid leukemia of AEs (Table 5). This finding was in line with the drug specifications. Although autoimmune hemolytic anemia and aplastic anemia were reported, these were not listed in the drug specifications. These newly identified ADRs will be valuable for clinicians. Drug-induced immune hemolytic anemia is a rare and serious complication in the treatment of blood disorders [10,11]. More than 100 drugs have been associated with immune hemolytic anemia [12]. Neta reported that 5 (16%) of 31 patients with chronic lymphocytic leukemia receiving bendamustine developed some degree of hemolysis. This is possibly related to the combined alkylating and purine analogue properties of the drug. Immune hemolytic anemia previously associated with fludarabine may be a risk factor for bendamustine-induced hemolysis.

Notably, long-term use of bendamustine has been associated with an increased risk of cytomegalovirus (CMV) infection and reactivation of a previous CMV infection. A retrospective study observed a frequency of CMV viral reactivation of up to 19% [13]. This may be attributed to the attenuation of immune response by bendamustine, making patients vulnerable to opportunistic infections, including cytomegalovirus reactivation. However, another study found no difference in the incidence of CMV reactivation at any stage in patients with lymphoma who received a bendamustine-containing regimen as a first-line therapy [14]. This supports the likelihood that viral reactivation is related to immune damage induced by chemotherapeutic agents rather than by the disease itself. Moreover, the incidence of CMV reactivation is high among older adults (aged >60 years) with newly diagnosed and relapsed/refractory inert and invasive disease treated with bendamustine-containing regimens and CMV lesions in the liver, gastrointestinal tract, lungs, or retina [15]. Therefore, early and close monitoring of clinical and laboratory findings in elderly hematologic patients treated with bendamustine may improve the clinical management and prognosis of these patients. In addition to viral infections [16], invasive fungal and bacterial infections have been reported to be caused by bendamustine [13,17]. This study supported this finding and reported that AEs such as fungal pneumonitis, bronchopulmonary aspergillosis, Aspergillus infections, and bacterial infections are not documented in the drug package inserts. This highlights the need for clinical attention to the signs of infection and use of appropriate anti-infective prophylaxis when necessary.

Bendamustine has potent immunosuppressive effects and can lead to reactivation of hepatitis B virus (HBV) [18,19]. Yoshiki has reported two cases of lymphoma patients with reactivation of preexisting HBV infections due to bendamustine chemotherapy, In these patients, prompt treatment with entecavir resulted in a rapid turnaround of HBV DNA levels and prevented its progression [20]. However, HBV reactivation has also been reported due to bendamustine and prophylactic entecavir administration, and entecavir has been associated with mortality in patients with HBV reactivation due to increased lactic acidosis and encephalopathy [21]. This suggests that caution should be exercised when using entecavir as preemptive therapy. This study found AE-related signs of HBV and HBV reactivation among the AE reports, consistent with the drug specifications, suggesting the need for close clinical monitoring of HBV DNA levels during bendamustine treatment.

Cutaneous AEs are concern during bendamustine treatment. A clinical trial showed that the occurrence of bendamustine-related skin AEs, in descending order of frequency, are infusion-related reactions (ROR = 5.708), herpes zoster (ROR = 4.658), allergy (ROR = 3.271), and rash (ROR = 1.472) [22]. In this study, the strongest associations found were infusion site vesicles (ROR = 63.66), infusion site discoloration (ROR = 49.27), infusion site erythema (ROR = 17.81), and Stevens – Johnson syndrome (ROR = 12.83), in that order. It was considered to be related to the extraction of the database and the number of reported cases. Lysis of toxic skin necrosis has also been reported in clinical trials and post-commercialization [23]. No signal intensity for toxic skin necrolysis was found in our study. We believe that it reflects underreporting of life-threatening toxic reactions such as Stevens – Johnson syndrome and toxic epidermal necrolysis and this question needs to be explored further.

Of the respiratory, thoracic, and mediastinal diseases found in our analysis, Pneumocystis jirovecii pneumonia, and diffuse

alveolar injury were mentioned in the drug specifications. A retrospective study found that, among adult cases of NHL treated with bendamustine and a CD20-targeted monoclonal antibody (rituximab or ofatumumab), the Pneumocystis jirovecii pneumonia infection rate was 6% [2]. Another single-center retrospective cohort study [24] showed a cumulative incidence of Pneumocystis carinii pneumonia of 1.7% (95%CI 0.8%–3.3%; maximum follow-up of 2.5 years) after initiation of bendamustine. Additionally, pleural effusion, coronavirus infection, occlusive bronchiectasis, *Pseudomonas aeruginosa*-induced pneumonia, pneumococcal pneumonia, and spontaneous pneumothorax were identified in this analysis. These are newly identified serious AEs to bendamustine that are not documented in the drug specifications. Among these, pleural effusion had the highest incidence ($n = 48$) and was highly correlated with the signal intensities of ROR 4.75 (3.54–6.37), PRR 4.71 (3.52–6.3), IC025 2.23 (1.28), and EBGM 4.7 (3.5).

Other severe AEs identified for the first time in this study were progressive multifocal leukoencephalopathy (PML), Guillain – Barré syndrome, and demyelinating polyneuropathy. PML [25] is a rare and severe central nervous system disease [26,27] caused by John Cunningham (JC) virus infection [28]. High-intensity signals of JC virus infection were consistently found in our analysis in infectious and invasive diseases with an ROR of 18.36 (6.86–49.11), PRR 18.34 (6.86–49.02), IC025 4.19 (1.52), and EBGM 18.21 (6.81). T-cell defects are a major contributor to drug-associated PML and a common risk factor [29]. Such T-cell defects may result from decreased T-cell counts due to bendamustine. $CD4^+$ T-cells play a central role in the control of intracerebral JC virus [30]. $CD4^+$ T-cells and Th1 cells act synergistically to control the dissemination of intracerebral JC virus infection by driving the activation and proliferation of $CD8^+$ T-cells, which ultimately direct the production of JC virus-specific effector cells [29,31]. Therefore, when patients treated with bendamustine develop unexplained neurologic symptoms, they should undergo prompt magnetic resonance imaging to facilitate the swift diagnosis of JC virus in the cerebrospinal fluid by polymerase chain reaction.

5. Limitations

Our study had several limitations. First, FAERS data comes from a voluntary reporting system, which may be subject to incomplete reports and biases. Second, because some drugs are used more often than others, reports of AEs associated with them will show corresponding differences in frequency, resulting in the potential over- and underestimation of the incidences of AE. Third, there is no comparison or control group, making it difficult to determine whether the ADRs associated with bendamustine use are higher than the expected baseline risk or not. Fourth, the data provided by FAERS show only correlations between the occurrence of ADRs and the use of a particular drug, they do not prove the direct causal relationship. Demonstrating causality will require further clinical studies and evaluation. Fifth, in clinical practice, most adverse drug reactions, especially rare complications and infectious complications, occur during the combined treatment with bendamustine. Therefore, it is difficult to clearly separate them, and further clinical research is needed to confirm this.

6. Conclusion

This study scientifically and quantitatively analyzed the AE risks of bendamustine using reports from the FAERS database. Unexpected and previously unidentified major AEs were identified, including autoimmune hemolytic anemia, pleural effusion, PML, and JC virus. Hematologic and cutaneous reactions, infections, and infusion reactions were found to be common AEs that should be of great concern. This research provides a reference for clinicians and a springboard for further research. It is recommended to closely monitor the infusion sites and skin changes of patients during the clinical use of bendamustine. Dynamic monitoring of blood routine, coagulation function, inflammatory markers, ultrasound, and imaging examinations is essential to promptly detect possible adverse drug reactions caused by the medication. Early intervention should be taken to minimize the associated risks that may occur during the course of treatment.

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Author contribution

Q Huang: conceptualization, methodology, execution, acquisition of data, analysis and interpretation, writing original and revised draft; Y Wu: methodology, formal analysis, Validation, draft proofreading; H Li: conceptualization, study design, supervision, Writing original and revised draft.

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