Research Letter

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Safety evaluation of inotuzumab ozogamicin: a pharmacovigilance study based on the FAERS database

Xueyu Duan, MSc, Yongkun Deng, BSc*, Lei Li, BSc, Zhaoheng Yin, BSc, Limei Yu, BSc

Objective: Given inotuzumab ozogamicin (InO) relatively recent market introduction and ongoing new drug surveillance period, further research is needed on its adverse drug events (ADEs) in the real world.
Methods: Retrieve and analyze ADE reports associated with InO from the FAERS database, covering the period from 2004Q1 to 2024Q3, and employ the reporting odds ratio (ROR) methodology to conduct signal detection for InO-related ADEs.
Results: This study analyzed 1007 (2725 ADEs) patients, focusing on critical issues like veno-occlusive liver disease (VOD) (n = 97, ROR = 486.02), infections (n = 20, ROR = 3.27), and febrile neutropenia (n = 57, ROR = 20.43). Additionally, it also revealed some new ADEs, including sepsis (n = 35, ROR = 7.14), cytokine release syndrome (n = 22, ROR = 36.78), graft-versus-host disease (n = 20, ROR = 62.21), enterocolitis infectious (n = 3, ROR = 69.07), pneumonia fungal (n = 6, ROR = 30.76), and multiple organ dysfunction syndrome (n = 21, ROR = 10.65), among others. Consequently, it is imperative to exercise increased vigilance regarding these potential ADEs in the clinical administration of InO.
Conclusion: This study underscores the potential ADEs and associated risks with the clinical application of InO, with particular emphasis on the risks of VOD, infections, and febrile neutropenia. The implementation of a vigilant monitoring strategy is crucial for the early detection and timely management of these potential complications.

Keywords: adverse drug event, FAERS, inotuzumab ozogamicin, ROR

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant neoplasm of the hematopoietic system, including B-ALL and T-ALL. For many years, the treatment of adult B-ALL has primarily relied on multi-drug combination cytotoxic chemotherapy. Although approximately 80%–90% of patients achieve remission through these treatment regimens, a significant proportion still experience disease relapse[1,2]. Adult patients with relapsed or refractory (R/R) B-ALL often struggle to achieve optimal therapeutic outcomes. Various treatment strategies have been developed for this disease, including tyrosine kinase inhibitors (TKIs), immunotherapy, and chimeric antigen receptor (CAR) T-cell therapy. While these approaches can alleviate the disease to some extent, treatment-related toxicities are commonly observed[3,4]. Therefore, despite certain advancements in the field, patients with R/R B-ALL remain in urgent need of safer and more effective treatment strategies.

Inotuzumab ozogamicin (InO) is a CD22-targeting antibody-drug conjugate (ADC) comprising three elements: a humanized IgG4 kappa antibody (inotuzumab), N-acetyl-gamma-calicheamicin, and an acid-cleavable linker. As a novel targeted therapy, InO has shown significant efficacy in treating R/R ALL,

HIGHLIGHTS

- The study utilized the FAERS database, combining data mining and statistical analysis to systematically identify and evaluate potential adverse drug events (ADEs) associated with inotuzumab ozogamicin (InO) in clinical applications.
- InO demonstrated significant efficacy in treating R/R B-ALL, but it was accompanied by various ADEs, including veno-occlusive liver disease, infection, febrile neutropenia, and cytopenia.
- The investigation uncovered a range of new ADEs, such as sepsis, CRS, GVHD, and encephalopathy, highlighting the need for increased clinical awareness and timely management strategies.
- Emphasizes the crucial importance of thorough risk assessment and ongoing vigilance in clinical practice for both elderly and pediatric patients.
- Possibility of exploring combining or sequencing InO with tyrosine kinase inhibitors or other treatments to optimize outcomes and enhance safety.

Department of Pharmacy, The 926th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army, Kaiyuan, Yunnan, China

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: Department of Pharmacy, The 926th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army, Kaiyuan, Yunnan 691600, China. Tel.: +86 18988359003. E-mail: 745763076@qq.com (Y. Deng).*

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achieving high complete remission (CR/CRi) and minimal residual disease negativity (MRD) rates, making it a valuable clinical option[5–7]. Its mechanism involves binding to CD22-positive tumor cells, internalization, and linker hydrolysis in acidic intracellular conditions, releasing active N-acetyl-gamma-calicheamicin dimethylhydrazine to induce DNA double-strand breaks, cell cycle arrest, and apoptosis[8]. In recent years, numerous clinical studies have further confirmed the outstanding efficacy of InO in the treatment of R/R ALL[9,10]. However, clinical observations indicate that ALL patients may experience ADEs such as nausea, headache, fever, and neutropenia following InO treatment[11–13], posing significant risks to patient safety. Given the relatively short time since InO's market approval and its status within the new drug monitoring period, systematic evaluation and comprehensive analysis of its ADE profile are of critical importance for guiding rational clinical use and ensuring patient safety.

The FAERS database is a publicly accessible spontaneous reporting system and serves as a significant source of real-world data, providing valuable information for the monitoring and evaluation of ADEs[14]. Leveraging the extensive coverage and representativeness of this database, this study systematically analyzed the distribution characteristics and occurrence patterns of adverse reactions associated with InO in real-world clinical practice. The findings aim to offer evidence-based insights to guide the rational clinical use and safety assessment of this drug.

Methods

Data source

Data were extracted from the US FAERS database (2004Q1–2024Q3) using "Inotuzumab ozogamicin" and "Besponsa" as search terms. Seven data tables were collected: demographic and administrative information (DEMO), adverse reaction events (REAC), drug information (DRUG), patient outcomes (OUTC), reporting sources (RPSR), timing of drug therapy (THER), indications (INDI). Data were processed using SAS 9.4 for cleaning and analysis, with descriptive statistics applied to examine clinical characteristics, ADE frequencies, and outcomes.

Data processing

This study processed ADE reports using FDA-recommended methods. Key identifiers included: PRIMARYID (unique report identifier), CASEID (patient medical record number), and FDA_DT (report receipt date). Duplicate removal involved: (1) strictly followed FDA-recommended methods to exclude duplicate reports. For reports with multiple PRIMARYIDS, the record with the latest FDA_DT was retained. In cases where both CASEID and FDA_DT were identical, the report with the largest Primary value was preserved (Table 1); (2) for reports lacking unique or reliable identifiers, used key fields such as patient information, drug information, adverse event information, and report dates to identify duplicates; (3) for uncertain cases, conducted the manual review to ensure deduplication accuracy. ADE reports were classified and standardized using SAS 9.4 software and MedDRA 27.0, with SOC and PT classifications for InO-related events[15]. Initially, all quarterly DEMO data files were consolidated, and the most up-to-date information for each case was extracted. Subsequently, the data underwent standardization via drug name mapping, and the original disease and adverse event/medication error information were converted into Chinese to align with the terminology in the MedDRA dictionary. This standardization process also enabled the analysis of InO's distribution across various SOC categories. It is important to note that a single PT may correspond to multiple SOCs.

Table 1

Example of duplicate report removal criteria

CASEID	FDA_DT	PRIMARYID	Delete
4070800	20040113	4271953	Yes
4070800	20040113	4271960	Yes
4070800	20040130	4283861	Yes
4070800	20040308	4314767	No

Data analysis

This study employed the reporting odds ratio (ROR) method for InO ADE signal detection. The ROR method effectively synthesizes multi-study data, addressing heterogeneity in study design, sample characteristics, and ADE definitions. It provides robust, precise estimates, minimizing biases from simple data pooling, especially in small-sample or low-power studies. Furthermore, ROR identifies consistent ADE patterns across studies, offering valuable evidence for drug safety assessment and clinical decision-making[16]. Positive ROR signals are defined as: $a \geq 3$ reported target ADEs and a 95% confidence interval (CI) lower limit >1. Signal strength, reflecting the statistical association between InO and ADEs, increases with higher signal values. The ROR was computed using the following formula:

$$\frac{a/c}{b/d}=\frac{ad}{bc};\ \mathrm{ROR95\%CI}=e^{\ln(\mathrm{ROR})\pm1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

Results

Basic information of ADE reports for InO

Through screening and matching, we obtained 1007 cases of ADEs reported by patients from 2004Q1 to 2024Q3, with a detailed breakdown of the various types of ADEs presented in Figure 1. Additionally, Table 2 provides a comprehensive overview of the demographic characteristics of the patients involved in these cases. Analysis of demographic data revealed a sustained upward trend in reported ADEs, particularly during the period from 2017 to 2022, which was significantly associated with the expanding use of medications ($P < 0.05$). Furthermore, significant variations in the incidence of ADEs were observed across different age groups and between genders. Figure 2 illustrates the reported timing of InO-related ADEs. Through the application of ROR analysis, a total of 115 ADE signals were successfully identified, with the top 50 ADEs ranked by signal strength systematically displayed in Table 3 and illustrated in Figure 3.

Mining of high-risk ADE signals in major SOCs for InO

This study, through systematic pharmacovigilance analysis, has uncovered significant safety risks associated with InO across multiple SOCs. In the hepatobiliary system, the drug has shown strong association signals with veno-occlusive liver

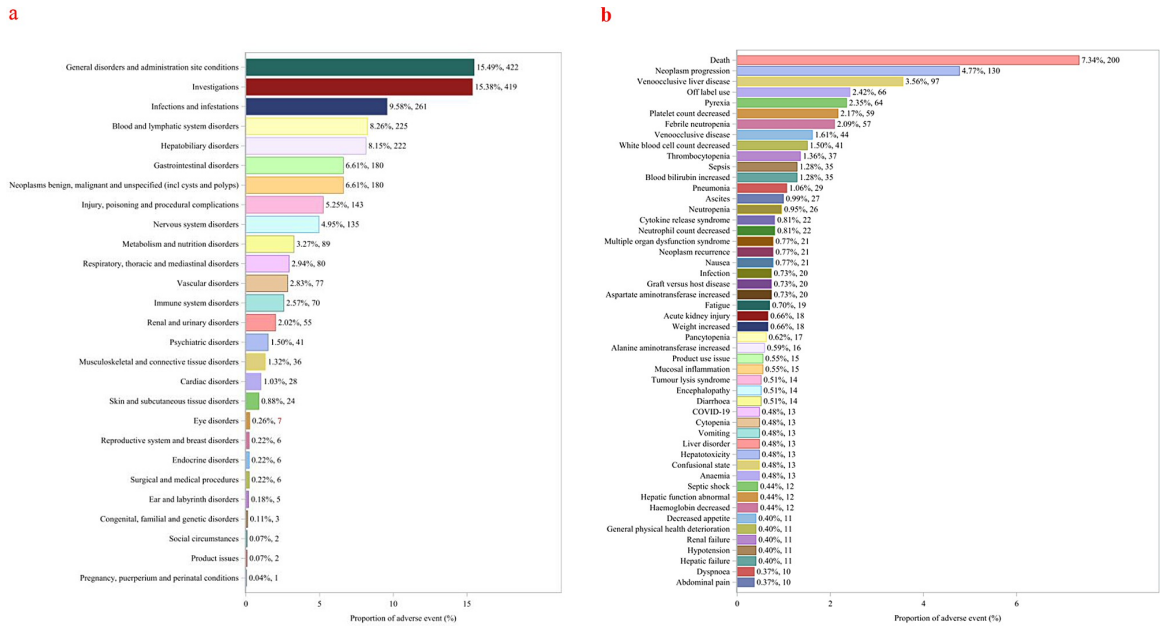

Figure 1. Distribution proportion of ADEs: (a) by SOC and (b) by PT. (a) Represents the proportional distribution of adverse events by SOC; (b) Shows the proportional distribution by PT. The color scheme distinguishes between individual PTs and their respective SOC, whereas the bar length quantitatively represents the incidence proportion for each ADE. SOC, System Organ Class; PT, Preferred Term.

disease (VOD) (ROR = 486.02, 95% CI: 395.96–596.57) and hepatorenal syndrome (ROR = 38.21, 95% CI: 12.30–118.69), with the risk of VOD being particularly prominent (Table 4). In the realm of infectious diseases, the data indicate that InO is strongly associated with sepsis (ROR = 7.14, 95% CI: 5.11–9.96) and infection (ROR = 3.27, 95% CI: 2.11–5.08), suggesting that patients may have an increased susceptibility to opportunistic infections (Table 5). Notably, in terms of hematological ADEs, InO is closely related to ADEs such as cytopenia (ROR = 28.49, 95% CI: 16.51–49.14), febrile neutropenia (ROR = 20.43, 95% CI: 15.72–26.57), and myelosuppression (ROR = 9.36, 95% CI: 5.03–17.42), indicating that patients may be at risk of severe immune function suppression (Table 6).

Additionally, we present a systematic analysis of ADEs affecting both the neurological and immunological systems, supplemented by specific case illustrations of medication administration to patients outside the recommended age parameters (Tables 7–9). In the context of nervous system disorders, ADEs linked to InO, including immune effector cell-associated neurotoxicity syndrome and encephalopathy, exhibit a significant association signal. Similarly, in the context of immune system disorders, strong associations were observed with graft-versus-host disease (GVHD) (ROR = 62.21, 95% CI: 40.04–96.65) and cytokine release syndrome (CRS) (ROR = 36.78, 95% CI: 24.17–55.98). These findings strongly suggest the necessity of establishing a comprehensive multisystem safety monitoring system during InO treatment, along with the formulation of corresponding risk prevention and control strategies.

Table 2

Demographic information on ADEs to InO

Index	Cases	Percentage (%)
Gender		
Male	450	44.69
Female	354	35.15
Not specified	203	20.16
Age		
<18	106	10.53
18–45	269	26.71
45–65	202	20.06
≥65	172	17.08
Not specified	258	25.62
Year		
2009	3	0.30
2012	5	0.50
2013	8	0.79
2014	6	0.60
2015	1	0.10
2017	27	2.68
2018	114	11.32
2019	126	12.51
2020	123	12.21
2021	167	16.58
2022	185	18.37
2023	142	14.10
2024	100	9.93
Reporter		
Physicians	614	60.97
Pharmacists	189	18.77
Consumers	143	14.20
Others	59	5.86
Not specified	2	0.20

Discussion

Pharmacovigilance research plays a crucial role in monitoring the safety of newly approved drugs. Although InO has demonstrated promising efficacy in clinical trials, its real-world safety profile requires further evaluation. Given the relatively recent

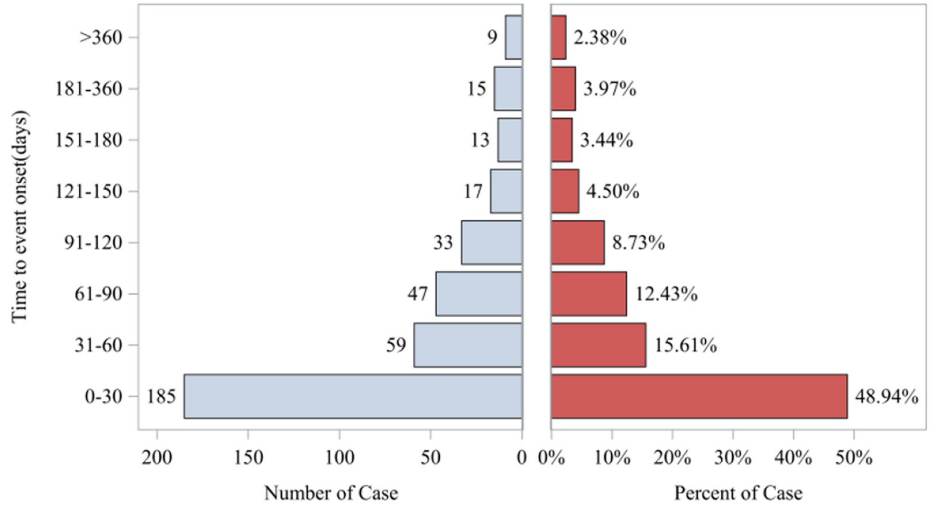

Figure 2. Time of occurrence of InO-related ADEs.

approval of this drug in China (NMPA approval in 2021), the identification of potential rare ADEs has become a key focus of current safety surveillance. This study systematically analyzes ADEs associated with InO using the FAERS database, aiming to provide evidence-based data to support clinical decision-making and regulatory risk management.

Basic information about InO

This pharmacovigilance study systematically analyzed 1007 reported cases of InO-associated ADEs across 27 SOCs. Although its indications primarily target adult patients, its application has gradually expanded to include patients of different age groups, including children and adolescents, in both clinical research and practice. A marked increase in ADE reports was observed between 2017 and 2022 ($P < 0.01$), potentially attributable to expanded InO utilization, improved pharmacovigilance awareness, and an 8.7% annual increase in disease incidence within approved indications[17]. Healthcare professionals constituted the primary reporting sources (physicians: 61.45%; pharmacists: 18.81%), highlighting the critical role of professional reporting systems. Furthermore, this study identified several high-priority therapeutic areas requiring intensified monitoring, including infectious diseases, hepatobiliary disorders, hematologic and lymphatic system abnormalities, along various neurological and immunological conditions. These findings are particularly significant given the complex pathophysiological mechanisms and potential for multisystem complications associated with these conditions. These evidence-based findings provide critical insights for developing risk-adapted therapeutic strategies and optimizing the benefit-risk profile of InO in clinical practice[18,19].

Table 3

115 ADE signals are classified by SOC

Adverse reaction signals (classification by SOC)	No.	Proportion (%)
General disorders and administration site conditions	5	4.35
Investigations	22	19.13
Infections and infestations	14	12.17
Blood and lymphatic system disorders	13	11.30
Hepatobiliary disorders	16	13.91
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	5	4.35
Gastrointestinal disorders	5	4.35
Injury, poisoning, and procedural complications	4	3.48
Nervous system disorders	7	6.09
Metabolism and nutrition disorders	5	4.35
Respiratory, thoracic, and mediastinal disorders	6	5.22
Vascular disorders	2	1.74
Immune system disorders	4	3.48
Renal and urinary disorders	2	1.74
Psychiatric disorders	2	1.74
Cardiac disorders	2	1.74
Surgical and medical procedures	1	0.87

Hepatic disorders

Hepatic sinusoidal obstruction syndrome (SOS), also known as VOD, is a primary focus of this study. This condition is frequently characterized by symptoms such as right upper quadrant pain, jaundice, hepatomegaly, and ascites, with a notably higher incidence following hematopoietic stem cell transplantation (HSCT)[20]. In the treatment of heavily pretreated patients with R/R CD22-positive B-ALL, InO has demonstrated favorable efficacy and tolerability. However, it is noteworthy that these patients developed SOS and cytopenia after undergoing HSCT[21]. Such ADEs have been explicitly documented in the prescribing information for InO, underscoring the necessity for clinicians to rigorously monitor liver function indicators, including ALT, AST, and total bilirubin levels. The INO-VATE study[13] demonstrated that InO treatment in patients with R/R B-ALL achieved a high CR/CRi and MRD negativity. However, SOS/VOD was identified as one of the potentially severe toxicities associated with InO, which aligns with the findings of this study. Split and smaller doses of InO reduce the risk of VOD/SOS[22,23]. A phase 4 trial[24] compared standard (1.8 mg/m^2) versus low-dose (1.2 mg/m^2) InO in high-risk R/R ALL patients, the results showed that 22 (ages 21–67) patients treated with the

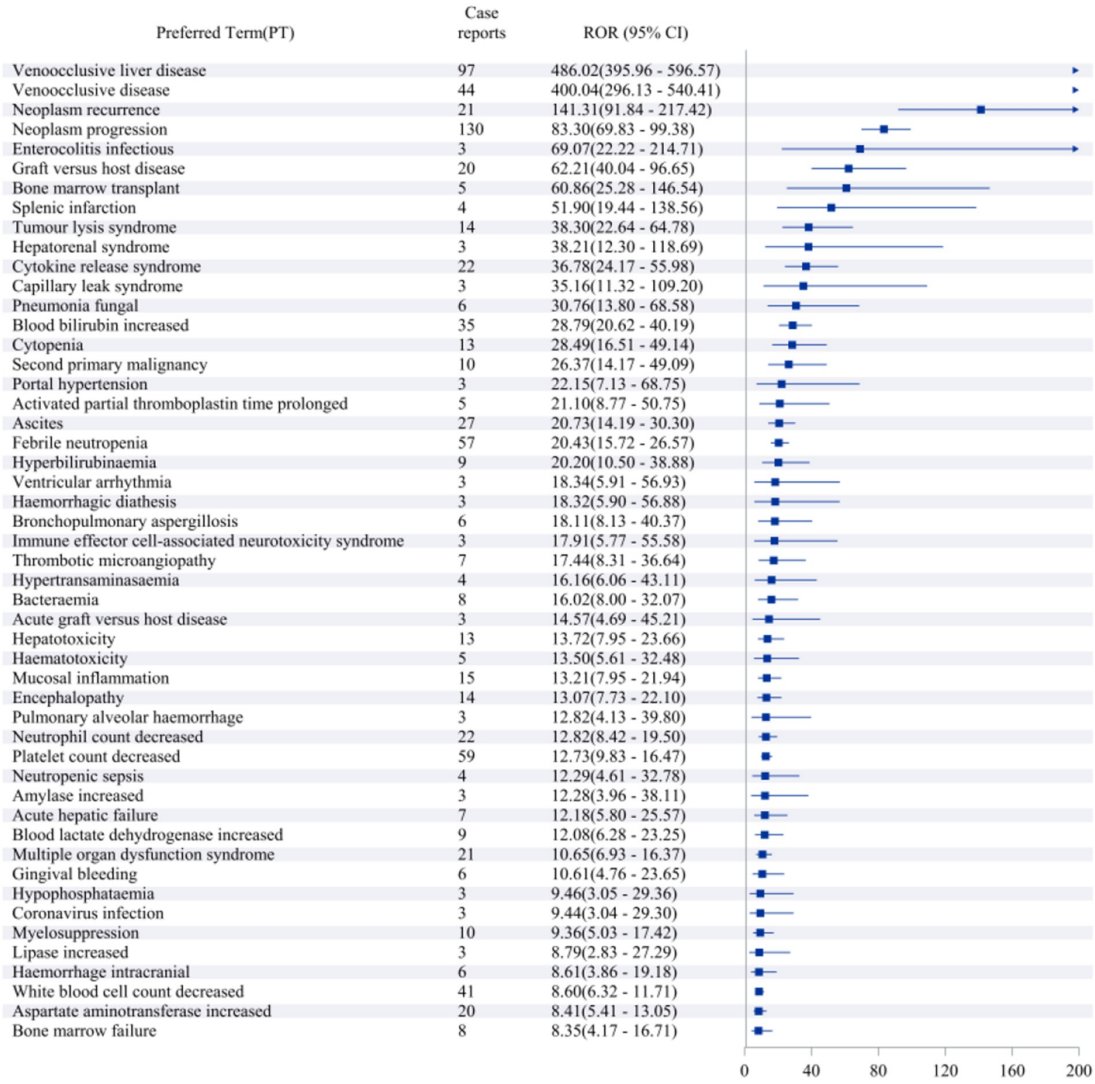

Figure 3. ROR values and signal intensity for high-risk PTs linked to InO-related ADEs. —, the range of the 95% confidence interval; →, the value displayed exceeds the highest value on the chart; ■, ROR value; ▲, lower CI limit > scale upper limit; — and ▲, upper ROR CI limit > scale upper limit; 95% CI, 95% confidence interval; ROR, reporting odds risks.

low dose achieved 50% CR/CRi, with 73% of responders being MRD-negative, revealed that the InO dose-fractionation regimen exhibited comparable efficacy while significantly reducing the risk of SOS/VOD[25,26]. To minimize SOS/VOD risk, limiting InO to two doses and avoiding double alkylating agents or hepatotoxic drugs before HSCT is recommended[27]. Pretreatment liver function tests and prophylactic ursodeoxycholic acid are advised. Treatment should be paused if bilirubin rises to 1.3–1.5 mg/dl, with consideration of high-dose corticosteroids[28]. Clinically, InO dosing is tailored to patient-specific factors (age, weight, disease stage), with close monitoring of hematological parameters, infections, and complications to optimize treatment.

Furthermore, a phase I clinical trial revealed[27] that among 58 patients treated with InO followed by allogeneic HSCT, 17 patients developed VOD/SOS, with 53% of these cases tragically resulting in mortality due to concurrent multiorgan failure. This phenomenon is believed to be linked to the combination of InO treatment and HSCT in patients with B-ALL[29]. Notably, HSCT remains a potentially curative option for elderly patients with R/R ALL. In the context of R/R disease, if HSCT is planned, the post-InO treatment regimen must be carefully designed to mitigate the risk of SOS[19]. Alternatively, if CAR-T therapy is chosen, attention must be paid to the potential issue of B-cell aplasia. Thus, in clinical InO use, assessing VOD/SOS risk factors and adopting preventive measures, such as avoiding hepatotoxic drugs and monitoring liver function, are essential to reduce post-HSCT occurrence.

Infections and infestations disorders

InO plays a pivotal role in the treatment of ALL; however, the associated risks of infection and sepsis demand heightened attention. This study revealed a notable association between InO and the occurrence of sepsis and infection. Studies have shown that this drug significantly improves CR/CRi rates and MRD

Table 4

Hepatobiliary reaction signals

PT	PT code	Events	ROR (95% CI)
Veno-occlusive liver disease	10047216	97	486.02 (395.96, 596.57)
Hepatorenal syndrome	10019846	3	38.21 (12.30, 118.69)
Portal hypertension	10036200	3	22.15 (7.13, 68.75)
Hyperbilirubinemia	10020578	9	20.20 (10.50, 38.88)
Hypertransaminasemia	10068237	4	16.16 (6.06, 43.11)
Hepatotoxicity	10019851	13	13.72 (7.95, 23.66)
Acute hepatic failure	10000804	7	12.18 (5.80, 25.57)
Hepatic failure	10019663	11	8.14 (4.50, 14.71)
Hepatic cytolysis	10049199	4	7.40 (2.77, 19.72)
Hepatic function abnormal	10019670	12	7.58 (4.30, 13.36)
Cholestasis	10008635	6	7.21 (3.24, 16.07)
Liver disorder	10024670	13	6.76 (3.92, 11.66)
Hepatomegaly	10019842	3	6.56 (2.11, 20.36)
Hepatic cirrhosis	10019641	4	5.05 (1.89, 13.46)
Jaundice	10023126	5	4.04 (1.68, 9.72)
Liver injury	10067125	3	3.29 (1.06, 10.22)

negativity rates, but its use is linked to an increased risk of infection and sepsis[21,30,31], which aligns with the findings of the current study. A phase 3 clinical trial involving high-risk B-ALL patients[32] further confirmed that InO may increase the risk of infection, particularly bacterial sepsis, with this risk being more pronounced in patients undergoing HSCT. Clinical trial data indicate that patients treated with InO often experience myelosuppression, particularly neutropenia and thrombocytopenia, which may lead to impaired immune function and a higher risk of infection. Additionally, chemotherapy following InO exposure can prolong bone marrow suppression and may induce hypogammaglobulinemia, further elevating the risk of bacterial infections. Although sepsis is not directly caused by drug infusion, subsequent treatments may exacerbate the risk of infection. Based on these findings, the study recommends prophylactic antibiotic use during periods of neutropenia, close monitoring of serum IgG levels, and timely supplementation therapy for patients with levels below 400 mg/dl to effectively reduce infection risks. Therefore, clinicians using InO must rigorously monitor patients' blood counts and immune function and implement preventive anti-infection measures when necessary. Furthermore, for sepsis patients, extending the infusion time of β-lactam antibiotics has been shown to improve pharmacologic target attainment rates[33] without increasing neurotoxicity or hepatorenal toxicity, which may provide valuable insights for infection management during InO treatment.

Table 5

Infection reaction signals

PT	PT code	Events	ROR (95% CI)
Enterocolitis infectious	10003997	3	69.07 (22.22, 214.71)
Pneumonia fungal	10049151	6	30.76 (13.80, 68.58)
Bronchopulmonary aspergillosis	10051905	6	18.11 (8.13, 40.37)
Bacteremia	10073755	8	16.02 (8.00, 32.07)
Neutropenic sepsis	10040047	4	12.29 (4.61, 32.78)
Coronavirus infection	10040070	3	9.44 (3.04, 29.30)
Pneumocystis jirovecii pneumonia	10009657	4	7.44 (2.79, 19.84)
Sepsis	10064687	35	7.14 (5.11, 9.96)
Septic shock	10021789	12	6.49 (3.68, 11.44)
Clostridium difficile colitis	10017533	3	6.40 (2.06, 19.87)
Device-related infection	10035664	4	5.30 (1.99, 14.14)
Infection	10003997	20	3.27 (2.11, 5.08)
Fungal infection	10049151	4	2.71 (1.02, 7.24)
Pneumonia	10051905	29	1.95 (1.35, 2.81)

Table 6

Blood and lymphatic reaction signals

PT	PT code	Events	ROR (95% CI)
Splenic infarction	10041648	4	51.90 (19.44, 138.56)
Cytopenia	10066274	13	28.49 (16.51, 49.14)
Febrile neutropenia	10016288	57	20.43 (15.72, 26.57)
Hemorrhagic diathesis	10062713	3	18.32 (5.90, 56.88)
Thrombotic microangiopathy	10043645	7	17.44 (8.31, 36.64)
Hepatotoxicity	10061188	5	13.50 (5.61, 32.48)
Myelosuppression	10028584	10	9.36 (5.03, 17.42)
Bone marrow failure	10065553	8	8.35 (4.17, 16.71)
Thrombocytopenia	10043554	37	7.68 (5.55, 10.62)
Hemolytic anemia	10018916	3	7.48 (2.41, 23.21)
Pancytopenia	10033661	17	7.02 (4.35, 11.30)
Disseminated intravascular coagulation	10013442	3	4.65 (1.50, 14.44)
Neutropenia	10029354	26	4.48 (3.04, 6.59)

Notably, the use of InO in pediatric and adolescent patients is associated with an increased incidence of sepsis[31]. Through the extraction and analysis of patient information, we found that the age range of patients receiving InO treatment was 3–17 years. An existing study[31] has shown that InO has a high remission rate in children and adolescents with R/R B-ALL, but the higher risk of infection and sepsis may be related to bone marrow suppression and immune function decline. Currently, clinical research data on InO in pediatric and adolescent patient populations remains relatively limited. Therefore, extra caution is required when developing treatment plans for this group. Potential risks should be thoroughly assessed, and monitoring and management during medication should be strengthened to ensure the safety and effectiveness of the treatment.

Blood and lymphatic disorders

Cytopenia and febrile neutropenia are ADEs that require close attention. Studies[13,34] demonstrated that the most common grade ≥3 ADEs associated with InO were neutropenia and thrombocytopenia, likely attributable to the suppressive effects of the drug's cytotoxic component on bone marrow function. These findings align with the results of the present study, further corroborating the reliability and scientific validity of our conclusions. Additionally, the AALL1621 study[21], revealed that 19.2% of patients experienced grade 3 or higher neutropenia

Table 7

Nervous reaction signals

PT	PT code	Events	ROR (95% CI)
Immune effector cell-associated neurotoxicity syndrome	10083347	3	17.91 (5.77, 55.58)
Encephalopathy	10014625	14	13.07 (7.73, 22.10)
Hemorrhage intracranial	10018985	6	8.61 (3.86, 19.18)
Hepatic encephalopathy	10019660	3	7.05 (2.27, 21.89)
Neurotoxicity	10029350	3	4.16 (1.34, 12.91)
Cerebral hemorrhage	10008111	6	3.74 (1.68, 8.33)
Altered state of consciousness	10001854	3	3.26 (1.06, 10.13)

Table 8

Immune system reaction signals

PT	PT code	Events	ROR (95% CI)
Graft versus host disease	10018651	20	62.21 (40.04, 96.65)
Cytokine release syndrome	10052015	22	36.78 (24.17, 55.98)
Acute graft versus host disease	10066260	3	14.57 (4.69, 45.21)
Hemophagocytic lymphohistiocytosis	10071583	3	7.44 (2.40, 23.10)

and/or thrombocytopenia during the second treatment cycle, indicating that clinicians need to pay particular attention to the potential impact of InO on blood cell counts and implement effective measures to prevent and manage possible infection risks. As InO, an ADC, may disrupt normal blood cell function and increase infection risks during treatment, clinicians should closely monitor hematologic parameters in patients receiving InO, including regular blood cell count checks, and promptly initiate preventive and therapeutic measures upon detecting signs of infection to ensure patient safety and treatment efficacy.

Novel ADEs identified

Additionally, this study identified ADEs associated with InO that were not previously mentioned in the literature or prescribing information, including sepsis, CRS, GVHD, encephalopathy, and infectious enterocolitis. These findings warrant significant clinical attention. Among these, GVHD, although reported in fewer cases, exhibited a notably strong signal and represents a key discovery in this study. GVHD, a major complication following HSCT, can affect multiple organ systems such as the gastrointestinal tract, liver, skin, and lungs[35]. Before HSCT, patients typically undergo preconditioning regimens involving chemotherapy and/or radiotherapy. InO, a monoclonal ADC-CD22, achieves its therapeutic effects via immunomodulatory mechanisms. When included in preconditioning regimens, InO may potentially interfere with post-transplant immune system reconstitution and homeostasis by modulating immune cell function or altering the immune microenvironment, thereby elevating the risk of GVHD[36,37]. Future research should investigate the role of InO within various transplantation preconditioning regimens and assess its impact on GVHD incidence. Current clinical data on the association between InO and GVHD remains limited, necessitating further clinical studies and extended follow-up to elucidate this relationship.

It is noteworthy that CRS, a common immune-mediated reaction in tumor immunotherapy, arises from the overactivation of lymphocytes such as B cells and T cells, as well as myeloid cells. This leads to the excessive release of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interferon-gamma, and interleukin-6 (IL-6). Clinically, CRS manifests as symptoms such as hypotension, hypoxia, and organ dysfunction[38]. Given the immunotherapeutic properties of InO, it releases cytotoxic agents to target and eliminate B cells by binding to and internalizing CD22. This mechanism may indirectly disrupt immune system homeostasis, leading to the overactivation of T cells and other immune cells, thereby triggering a significant release of cytokines (IL-6, TNF-α) and increasing the risk of CRS[28,39]. Consequently, clinical use of InO warrants careful monitoring of its potential impact on the immune system, particularly its propensity to induce an immunosuppressive state, which may compromise the patient's ability to defend against infections. Although InO has shown remarkable efficacy in treating B-ALL, its potential link to CRS necessitates further investigation. Future clinical research should prioritize elucidating InO's immune activation mechanisms, optimizing dosing strategies, and developing effective prevention and management protocols for CRS to enhance treatment outcomes and patient prognosis.

InO combined with other drugs to reduce ADEs

The incidence of ALL demonstrates a distinct bimodal distribution in both children and adults, with a peak incidence between 1 and 4 years of age[40,41]. Building on the demonstrated success of InO as a salvage monotherapy, extensive research efforts have been directed toward exploring its therapeutic potential in combination with low-intensity chemotherapy or other targeted ALL therapies, encompassing both salvage and frontline treatment approaches[42,43]. Studies have shown that the combination of InO with chemotherapy may significantly improve patients' response rates, depth of response, and duration, thereby creating opportunities for more patients to receive curative treatments

Table 9

Documentation of medication administration cases involving patients outside the approved age

Case id	Age	Gender	Weight (kg)	Drug name	Route	Dose (mg)	Dose form
13893679	8	M	26	InO	Intravenous	0.42	NA
14460780	16	M	60.2	InO	Intravenous	3.2	NA
14591017	16	F	52	Besponsa	Intravenous	4	Powder for solution for injection
15967742	8	M	26.5	InO	Intravenous	1	NA
19396780	6	M	19	InO	Intravenous	0.6	Powder for solution for injection
19711162	11	M	23.7	Besponsa	Intravenous	0.7	Powder for solution for injection
20214132	16	M	67.5	InO	Not Specified	0.95	NA
20988710	13	M	48.698	Besponsa	Intravenous	0.9	Powder for solution for injection
22202373	3	M	15.2	InO	Intravenous	0.32	NA
23029455	11	F	50	Besponsa	Intravenous	1	Powder for solution for injection
23100095	3	F	21.6	InO	Not Specified	0.4	NA
23397783	5	M	19.9	Besponsa	Intravenous	0.41	Powder for solution for infusion
24097359	17	F	62.993	Besponsa	Intravenous	1.5	Powder for solution for infusion
24133527	17	F	63.9	InO	Intravenous	0.94	Powder for solution for infusion

and potentially reducing the emergence of CD22-negative cells[21]. Furthermore, research indicates[44] that in the treatment of elderly patients with B-ALL, whether used alone or in combination with blinatumomab and low-intensity chemotherapy, InO can significantly improve progression-free survival. This finding suggests that reducing the intensity of chemotherapy may help enhance treatment tolerance in elderly patients while maintaining therapeutic efficacy. Another study[45] focused on the efficacy of InO in Philadelphia chromosome-positive (Ph+) R/R ALL patients, showing that InO is an important treatment option for achieving subsequent remission, especially for patients resistant to or refractory to prior TKI therapy. Additionally, TKIs can serve as maintenance therapy options after InO treatment and HSCT. Therefore, one of the important directions for future research is to explore the combination or sequential use of InO with TKIs or other treatment methods to further optimize therapeutic outcomes and improve safety.

Limitations

This study analyzed the FAERS database to assess the risk signals of ADEs linked to InO, offering insights into the safety profile of this novel drug. However, several limitations must be acknowledged. First, FAERS allows only preliminary single-drug analyses, limiting causality conclusions. Second, data may suffer from underreporting, duplication, omissions, and incomplete entries, with a focus on European/American populations, restricting ethnic variation insights. Third, due to study limitations, we did not perform a sensitivity analysis on deduplication methods. Future research should optimize deduplication by clearly describing the removal process and justifying methods, systematically assessing the impact of different strategies on ADE signal detection, and exploring alternatives like fuzzy matching or machine learning to compare their effects. Additionally, missing data precluded detailed analyses of factors such as dosage. Lastly, causality between InO and ADEs remains unestablished, requiring further investigation. Despite these constraints, the study provides valuable post-marketing insights into potential risks and clinical decision-making, emphasizing the need for vigilant monitoring to identify and manage InO-related ADEs.

Conclusions

This study, based on the FAERS database, employed a combination of data mining and statistical analysis methods to systematically identify and evaluate a series of potential ADEs associated with InO in clinical applications. The analysis revealed that InO demonstrates significant efficacy in treating R/R B-ALL, but is also accompanied by various ADEs, primarily including VOD, infection, febrile neutropenia, and cytopenia. It is of particular importance to highlight that InO may elevate the risk of SOS/VOD, necessitating vigilant and ongoing monitoring of patient status. Additionally, the investigation has unveiled a spectrum of novel ADEs such as sepsis, CRS, GVHD, and encephalopathy. These newly discovered ADEs underscore the need for heightened clinical awareness and prompt management strategies. Given InO's crucial role in treating R/R ALL, future large-scale, multicenter, prospective clinical studies are recommended to validate these findings, explore adverse reaction prevention and risk management strategies, and optimize treatment plans to enhance medication safety.

Ethical approval

This study used FDA public database data. Ethical approval was waived as it involved retrospective analysis of anonymized data without clinical trials or direct patient involvement, per institutional guidelines for secondary data analysis.

Consent

Not applicable.

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Author contributions

Methodology, writing – original draft, writing – review and editing: X.D.; writing – original draft: Y.D.; methodology: L.Y.; collected the data: L.L. and Z.Y.

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All authors declare no conflict of interest.

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