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RESEARCH ARTICLE

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Biomaterial-based drug delivery: evaluating the safety profiles of liposomal Vyxeos

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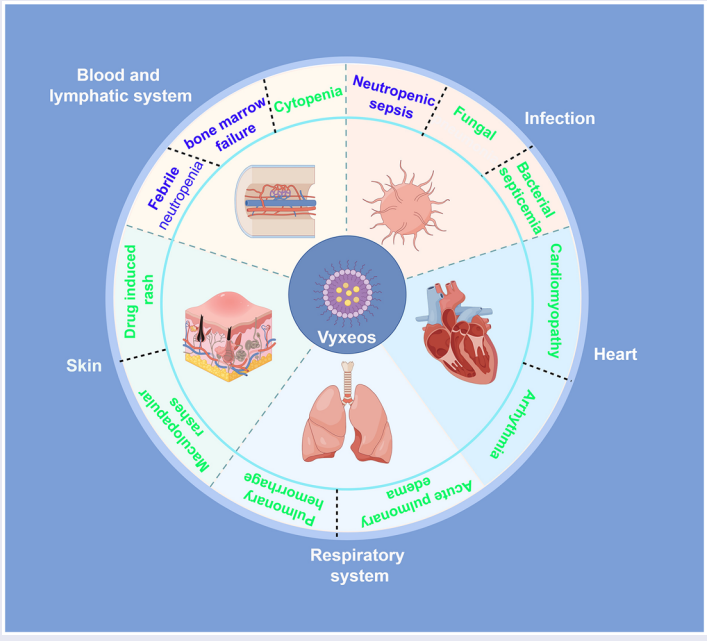
ABSTRACT

Vyxeos, a liposomal combination of cytarabine and daunorubicin, has improved survival outcomes for patients with high-risk acute myeloid leukemia (AML). However, its safety profile in real-world settings requires comprehensive evaluation. This study aims to assess the adverse event profiles associated with Vyxeos using data from the U.S. FDA's Adverse Event Reporting System (FAERS). A retrospective analysis of adverse event reports from the FAERS database was conducted for Vyxeos from January 2017 to June 2024. Reports were analyzed to assess patient demographics, system organ classes (SOCs), and preferred terms (PTs). Signal detection analysis was performed using disproportionality metrics, including Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-Item Gamma Poisson Shrinker (MGPS). A total of 1,036 reports were analyzed. The most frequently reported adverse events were hematologic (37.73%), infectious (28.42%), and cardiac disorders (13.22%). Febrile neutropenia, neutropenic sepsis, and pneumonia fungal were the most commonly reported events, with febrile neutropenia showing a strong association (ROR = 92.18). Males had a higher frequency of infectious events, while females reported more cardiac events. Most adverse events occurred within 30 days of treatment initiation, and 16.92% of reports involved hospitalization, while 18.33% reported death. Vyxeos is associated with significant hematologic, infectious, and cardiac adverse events. Close monitoring, infection prophylaxis, and cardiac assessments are recommended for patients receiving Vyxeos. Further research is needed to validate these findings and explore the mechanisms underlying the observed toxicities.

GRAPHICAL ABSTRACT



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Introduction

Vyxeos, also known as CPX-351, is a liposomal formulation of daunorubicin and cytarabine, approved for the treatment of adults with high-risk acute myeloid leukemia (AML), specifically therapy-related AML (t-AML) and AML with myelodysplasia-related changes (AML-MRC). This formulation was developed to improve the therapeutic outcomes for these specific AML subtypes, which are associated with poor prognosis. Vyxeos was approved by the FDA on August 3, 2017, and later received a positive opinion from the European Medicines Agency (EMA) in 2018 (Kyriaki et al. 2020; mAsya 2023).

Vyxeos demonstrated a significant improvement in overall survival compared to the standard '7 + 3' regimen of daunorubicin and cytarabine (7 days of cytarabine plus 3 days of daunorubicin). In a phase III trial, the median overall survival for patients treated with Vyxeos was 9.6 months, compared to 5.9 months for those on the standard regimen (hazard ratio, 0.69; 95% confidence interval, 0.52–0.90) (Kyriaki et al. 2020; mAsya 2023). The trial included 309 patients aged 60-75 years with newly diagnosed t-AML or AML-MRC, highlighting its efficacy in an older patient population with high-risk AML (mAsya 2023).

The liposomes are engineered to provide controlled interactions with components of the living system, thereby facilitating targeted delivery of the cytotoxic agents directly to leukemic cells while minimizing off-target effects. This form of drug delivery exemplifies the use of biomaterials to improve therapeutic outcomes through enhanced efficacy and reduced systemic toxicity. Such advances in the design of drug delivery vectors are underpinned by a combination of physical, chemical, and biological sciences, including polymer synthesis, nanotechnology, and the study of host responses to implanted materials.

The unique liposomal formulation is a carefully engineered biomaterial that allows for co-encapsulation of cytarabine and daunorubicin in a 5:1 molar ratio. This design aims to optimize synergistic cytotoxicity while reducing toxicity. Vyxeos is a fixed combination of daunorubicin and cytarabine encapsulated in liposomes, which allows for controlled release and potentially improved pharmacokinetics compared to non-liposomal formulations (Kyriaki et al. 2020). The formulation is designed to deliver the drugs at a synergistic ratio, enhancing their antineoplastic effects by inhibiting topoisomerase II activity and causing DNA damage (Kyriaki et al. 2020).

Despite its clinical benefits, Vyxeos has been associated with a range of adverse drug reactions (ADRs), some of which are severe and may limit its use in certain patient populations. The toxicity profile of Vyxeos is similar to the standard

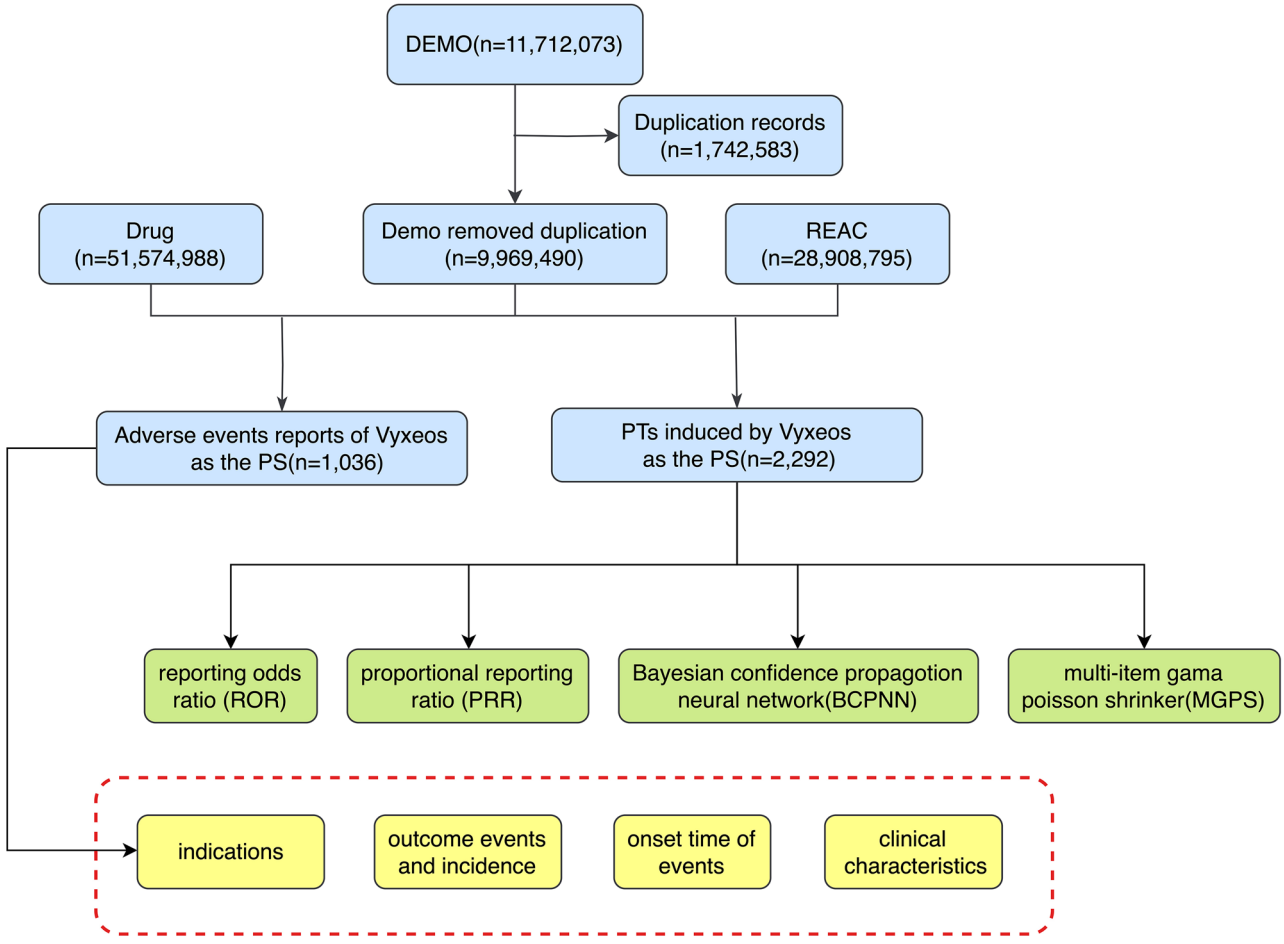

Figure 1. Flowchart of data extraction and analysis for adverse event reports related to vyxeos.
The diagram shows the stepwise reduction of records, starting from duplication removal to final extraction of patient records with relevant adverse events.

'7 + 3' regimen, with notable side effects including prolonged neutropenia and thrombocytopenia. Other common adverse effects include hypersensitivity reactions, febrile neutropenia, and gastrointestinal symptoms (Kyriaki et al. 2020; mAsya 2023). Evaluating the safety profile of Vyxeos is crucial for understanding its impact on patient management and optimizing therapeutic outcomes. The U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) serves as an invaluable tool for post-marketing safety surveillance, allowing for the identification and evaluation of potential ADRs that may not be fully characterized during clinical trials.

This study aims to explore the adverse event profiles associated with Vyxeos by analyzing data from the FAERS database. The FAERS database is particularly suitable for this analysis due to its large volume of real-world reports and its role in ongoing post-marketing safety monitoring. By assessing the frequency, severity, and demographics of reported ADRs, this study seeks to provide insights into the real-world safety profile of Vyxeos and to inform clinical decision-making for its use. Specifically, we investigate the distribution of system organ classes (SOCs) and preferred terms (PTs) related to Vyxeos, as well as perform subgroup analyses to identify risk patterns among different patient populations. This evaluation of post-marketing safety data will contribute to a more comprehensive understanding of Vyxeos' risk-benefit balance in the treatment of AML.

Methods

Data source

Data for this study were obtained from the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS). The FAERS database is a public repository that collects spontaneous reports of adverse events associated with various drugs. Data spanning from January 2017 to June 2024 were included in the analysis, covering all available reports involving Vyxeos as a primary suspect drug. Duplicate reports were identified and removed to ensure data accuracy (Figure 1).

Data extraction

The dataset was extracted using structured queries to identify adverse event reports where Vyxeos was listed as the primary suspect (PS). Information extracted included patient demographics (age, gender), event details, system organ classes (SOCs), preferred terms (PTs), reporting country, reporter type (consumer, healthcare professional), and outcomes (e.g. hospitalization, death, disability). Reports were cleaned to eliminate duplicates and inconsistencies, resulting in a final dataset of 1,036 reports for analysis.

Data analysis

Adverse events were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs). Signal detection analyses were performed using disproportionality metrics, including Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-Item Gamma Poisson Shrinker (MGPS). These metrics were used to assess the strength of the association between Vyxeos and the reported ADRs compared to other drugs in the FAERS database.

Subgroup analysis

Subgroup analyses were conducted to evaluate ADR profiles by patient demographics, such as age (categorized as <18, 18-60, and >60 years), gender (male, female), and geographic region. Additionally, time-to-onset of adverse events was assessed to determine the temporal relationship between Vyxeos administration and the occurrence of ADRs.

Statistical analysis

Descriptive statistics were used to summarize patient demographics and event characteristics. ROR and PRR values with 95% confidence intervals (CIs) were calculated to identify significant safety signals. Bayesian analysis using BCPNN and MGPS was performed to further validate the findings. A signal was considered significant if the lower limit of the 95% CI for ROR or PRR was greater than one. Data analyses were performed using R software (version 4.2.0), and visualizations were generated to illustrate the frequency distribution of SOCs and PTs, as well as the annual distribution of reports.

Table 1. Clinical characteristics of patients.

Variable	Total
Sex	
Female	304(29.34)
Male	377(36.39)
Unknown	355(34.27)
Age	
<18	27(2.61)
18 ~ 60	181(17.47)
> =60	328(31.66)
Unknow	500(48.26)
Reporter	
Consumer	409(39.48)
Pharmacist	292(28.19)
Physician	281(27.12)
Other health-professional	41(3.96)
Unknown	12(1.16)
Lawyer	1(0.10)
Reported countries	
United kingdom	299(28.86)
United states	261(25.19)
France	129(12.45)
Germany	115(11.10)
Italy	100(9.65)
Route	
Other	826(79.73)
Intravenous	197(19.02)
Intravenous drip	13(1.25)
Outcomes	
Other serious	803(59.84)
Death	246(18.33)
Hospitalization	227(16.92)
Life threatening	63(4.69)
Disability	3(0.22)

Ethical considerations

Since the FAERS database contains de-identified information and is publicly accessible, ethical approval was not required for this study.

Results

Patient demographics

The dataset comprised 1,036 reports involving Vyxeos as the primary suspect drug. Of these, 36.39% of cases were male, 29.34% were female, and 34.27% were of unknown gender (Table 1). The majority of patients were older than 60 years (31.66%), with 17.47% aged between 18 and 60 years, and 2.61% younger than 18 years. A large portion of reports (48.26%) did not specify the patient's age (Figure 2).

Annual distribution of adverse events

The annual distribution of adverse event reports involving Vyxeos showed a steady increase from 2017 to 2024, indicating increased usage and awareness of potential side effects over time (Figure 2). The number of reports peaked in 2023, reflecting heightened vigilance in post-marketing safety surveillance. Geographic analysis indicated that the majority of reports originated from the United Kingdom (28.86%), followed by the United States (25.19%) and France (12.45%) (Figure 2).

System organ class-level analysis

Adverse events were categorized by system organ class (SOC) (Table 2). The most commonly reported SOCs were blood and lymphatic system disorders (37.73%), infections and infestations (28.42%), and cardiac disorders (13.22%) (Figure 3). These findings suggest that Vyxeos is frequently associated with hematologic and infectious complications, consistent with its mechanism of action as a cytotoxic chemotherapy.

Preferred term-level analysis

The analysis of preferred terms (PTs) identified febrile neutropenia, neutropenic sepsis, and pneumonia fungal as the most frequently reported events (Table 3 and Figure 4). Febrile neutropenia had the highest reporting odds ratio (ROR = 92.18), indicating a strong association with Vyxeos treatment. Other significant ADRs included bone marrow failure and

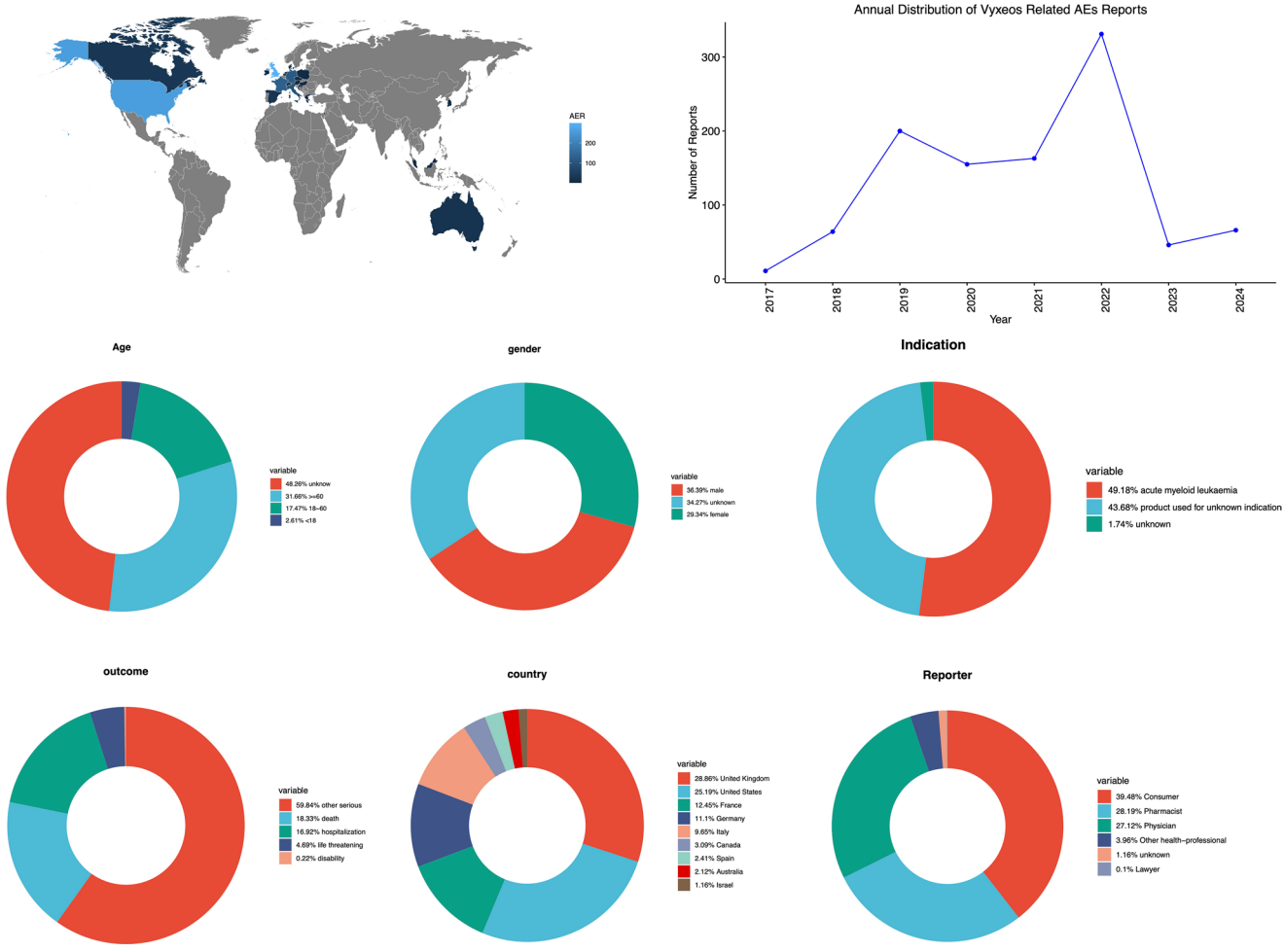

Figure 2. Annual distribution of adverse event reports for vyxeos from 2017 to 2024.
The figure shows an increase in the number of reports over time, reflecting enhanced awareness and monitoring of Vyxeos-related adverse events.

Table 2. Signal strength of reports at the system organ class level in the FAERS database.

Soc	Case reports	ROR(95% CI)	PRR(95% CI)	Chisq	IC(IC025)	EBGM(EBGM05)
Blood and lymphatic system disorders	391	11.54(10.35, 12.87)	9.74(8.83, 10.74)	3119.16	3.28(3.13)	9.73(8.89)
Infections and infestations	393	3.4(3.05, 3.79)	2.99(2.71, 3.3)	552.17	1.58(1.43)	2.99(2.73)
Cardiac disorders	137	2.93(2.47, 3.48)	2.81(2.4, 3.29)	163.71	1.49(1.24)	2.81(2.44)
Congenital, familial and genetic disorders	9	1.37(0.71, 2.63)	1.37(0.72, 2.62)	0.89	0.45(-0.45)	1.37(0.79)
Respiratory, thoracic and mediastinal disorders	126	1.16(0.97, 1.39)	1.16(0.97, 1.38)	2.76	0.21(-0.05)	1.16(0.99)
Skin and subcutaneous tissue disorders	153	1.1(0.93, 1.3)	1.09(0.93, 1.28)	1.28	0.13(-0.11)	1.09(0.95)
Vascular disorders	44	0.98(0.73, 1.32)	0.98(0.73, 1.31)	0.02	−0.03(-0.46)	0.98(0.76)
Renal and urinary disorders	46	0.95(0.71, 1.27)	0.95(0.71, 1.27)	0.13	−0.08(-0.49)	0.95(0.74)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	68	0.85(0.67, 1.08)	0.85(0.67, 1.08)	1.74	−0.23(-0.57)	0.85(0.7)
General disorders and administration site conditions	355	0.82(0.73, 0.91)	0.84(0.76, 0.93)	12.54	−0.24(-0.41)	0.84(0.77)
Hepatobiliary disorders	16	0.8(0.49, 1.31)	0.8(0.49, 1.31)	0.79	−0.32(-1.01)	0.8(0.53)
Investigations	111	0.79(0.65, 0.96)	0.8(0.67, 0.95)	5.84	−0.32(-0.59)	0.8(0.68)
Gastrointestinal disorders	137	0.69(0.58, 0.82)	0.71(0.61, 0.83)	17.5	−0.49(-0.74)	0.71(0.62)
Metabolism and nutrition disorders	31	0.65(0.46, 0.93)	0.66(0.46, 0.94)	5.61	−0.6(-1.11)	0.66(0.49)
Immune system disorders	14	0.47(0.28, 0.8)	0.48(0.28, 0.81)	8.22	−1.07(-1.81)	0.48(0.31)
Injury, poisoning and procedural complications	127	0.43(0.36, 0.51)	0.46(0.39, 0.55)	92.68	−1.13(-1.38)	0.46(0.39)
Reproductive system and breast disorders	6	0.39(0.17, 0.86)	0.39(0.17, 0.87)	5.87	−1.37(-2.44)	0.39(0.2)
Nervous system disorders	69	0.36(0.28, 0.46)	0.38(0.3, 0.48)	75.28	−1.39(-1.73)	0.38(0.31)
Eye disorders	14	0.3(0.18, 0.51)	0.3(0.18, 0.51)	22.75	−1.72(-2.45)	0.3(0.2)
Musculoskeletal and connective tissue disorders	30	0.24(0.16, 0.34)	0.25(0.18, 0.36)	73.34	−2.02(-2.54)	0.25(0.18)
Psychiatric disorders	14	0.1(0.06, 0.18)	0.11(0.06, 0.19)	106.89	−3.19(-3.92)	0.11(0.07)

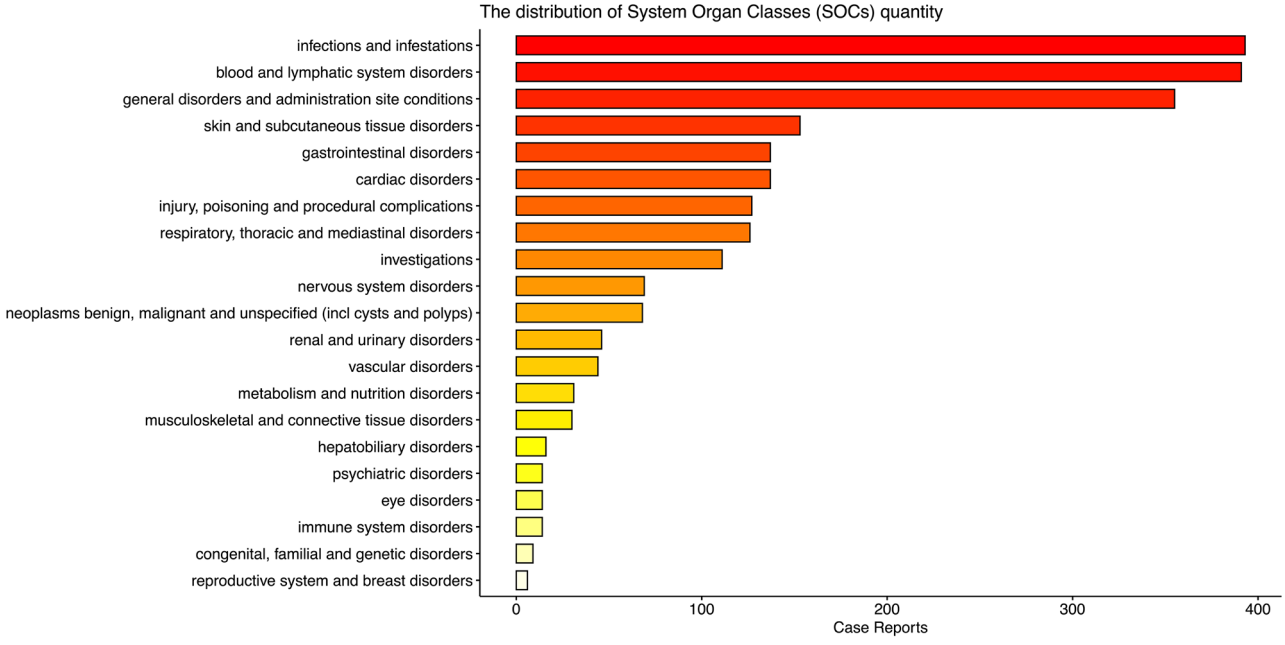

Figure 3. Distribution of system organ classes (SOCs) for vyxeos-related adverse events.
Blood and lymphatic system disorders, infections, and cardiac disorders were the most frequently reported SOCs, highlighting the hematologic and infectious complications associated with Vyxeos.

acute myeloid leukemia relapse, highlighting the severe and complex nature of adverse events linked to this therapy.

Signal detection analysis

Signal detection analysis was performed using ROR, PRR, BCPNN, and MGPS. Significant safety signals were detected for febrile neutropenia, bacteremia, and sepsis (Table 3 and Figure 5). The ROR values for febrile neutropenia (ROR = 92.18, 95% CI: 80.19-105.97) and bacteremia (ROR = 64.8, 95% CI: 44.89-93.56) indicate strong associations with Vyxeos use. These signals warrant further investigation to better understand the risk factors contributing to these adverse events.

Subgroup analysis

Subgroup analyses revealed that males had a higher frequency of reported ADRs, particularly for infections such as

Table 3. Top 30 signal strength of reports at the preferred term level in the FAERS database.

Soc	pt	Case reports	ROR(95% CI)	PRR(95% CI)	Chisq	IC(IC025)	EBGM(EBGM05)
Infections and infestations	Neutropenic sepsis	24	95.28(63.63, 142.67)	94.29(63.71, 139.54)	2199.13	6.55(5.98)	93.6(66.77)
	Bacteremia	29	64.8(44.89, 93.56)	64(44.97, 91.07)	1789.66	5.99(5.47)	63.68(46.83)
	Pneumonia fungal	9	53.72(27.88, 103.53)	53.52(28.03, 102.19)	461.89	5.74(4.84)	53.29(30.78)
	Escherichia sepsis	5	50.8(21.09, 122.38)	50.69(20.98, 122.45)	242.59	5.66(4.5)	50.49(24.19)
	Escherichia bacteremia	4	41.69(15.61, 111.37)	41.62(15.62, 110.89)	158.07	5.37(4.11)	41.49(18.24)
	Catheter site infection	3	27.98(9.01, 86.93)	27.94(8.96, 87.08)	77.77	4.8(3.38)	27.88(10.8)
	Arthritis bacterial	4	26.42(9.9, 70.51)	26.37(9.9, 70.26)	97.44	4.72(3.45)	26.32(11.57)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukemia refractory	12	1300.33(716.84, 2358.79)	1293.53(718.47, 2328.85)	14056.72	10.2(9.37)	1173.29(712.85)
	Leukemia recurrent	6	112.9(50.49, 252.46)	112.61(50.42, 251.52)	657.83	6.8(5.73)	111.62(56.92)
	Acute myeloid leukemia recurrent	6	70.64(31.63, 157.75)	70.46(31.55, 157.38)	408.56	6.13(5.06)	70.07(35.77)
	Acute myeloid leukemia	26	47.08(31.96, 69.35)	46.56(31.46, 68.91)	1155.09	5.54(4.99)	46.39(33.55)
Investigations	Blood copper increased	3	498.49(157.14, 1581.35)	497.84(156.63, 1582.37)	1431.04	8.9(7.45)	478.97(182.3)
	Electrocardiogram t wave abnormal	7	179.62(85.09, 379.18)	179.07(85.03, 377.13)	1222.22	7.46(6.45)	176.58(94.5)
	Blast cell count increased	5	114.9(47.59, 277.42)	114.65(47.46, 276.96)	558.25	6.83(5.67)	113.63(54.35)
	Ejection fraction decreased	17	26.79(16.62, 43.2)	26.6(16.62, 42.58)	418.09	4.73(4.06)	26.55(17.8)
Blood and lymphatic system disorders	Febrile neutropenia	220	92.18(80.19, 105.97)	83.43(74.17, 93.84)	17820.06	6.37(6.17)	82.89(73.76)
	Febrile bone marrow aplasia	12	68.28(38.66, 120.59)	67.93(38.48, 119.93)	787.13	6.08(5.29)	67.57(41.98)
	Bone marrow failure	25	32.98(22.22, 48.94)	32.63(22.05, 48.29)	764.78	5.02(4.47)	32.55(23.39)
	Cytopenia	16	26.79(16.38, 43.83)	26.61(16.3, 43.44)	393.7	4.73(4.04)	26.56(17.59)
Skin and subcutaneous tissue disorders	Acute febrile neutrophilic dermatosis	3	36.32(11.69, 112.89)	36.28(11.64, 113.08)	102.62	5.18(3.76)	36.17(14.01)
	Toxic skin eruption	9	24.82(12.89, 47.79)	24.72(12.95, 47.2)	204.51	4.63(3.73)	24.68(14.26)
	Rash maculo-papular	20	24.05(15.48, 37.36)	23.85(15.5, 36.71)	437.13	4.57(3.95)	23.8(16.46)
Respiratory, thoracic and mediastinal disorders	Acute pulmonary edema	12	74.17(41.99, 131.02)	73.79(41.8, 130.27)	856.69	6.2(5.41)	73.37(45.58)
	Pulmonary hemorrhage	5	20.18(8.38, 48.55)	20.13(8.33, 48.63)	90.78	4.33(3.17)	20.1(9.64)
Metabolism and nutrition disorders	Tumour lysis syndrome	9	24.53(12.74, 47.24)	24.44(12.8, 46.67)	201.98	4.61(3.71)	24.4(14.1)
Injury, poisoning and procedural complications	Craniofacial fracture	4	198.18(73.75, 532.55)	197.83(74.25, 527.11)	771.26	7.61(6.33)	194.79(85.18)
General disorders and administration site conditions	Mucosal inflammation	20	20.59(13.25, 31.99)	20.42(13.27, 31.43)	368.92	4.35(3.73)	20.39(14.1)
Gastrointestinal disorders	Neutropenic colitis	4	43.15(16.16, 115.27)	43.08(16.17, 114.78)	163.86	5.42(4.16)	42.94(18.87)
Congenital, familial and genetic disorders	Aplasia	9	98.23(50.92, 189.52)	97.85(51.25, 186.84)	856.14	6.6(5.7)	97.11(56.03)
Cardiac disorders	Cardiomyopathy	10	22.09(11.87, 41.14)	22(11.75, 41.19)	200.17	4.46(3.6)	21.97(13.06)

neutropenic sepsis and bacteremia (Tables 4 and 5). Females, on the other hand, showed a higher incidence of cardiac events, such as arrhythmia and pericarditis (Table 4).

Time to onset of adverse events

The time to onset of adverse events varied significantly among patients (Figure 6). Most ADRs occurred within the first 30 days of Vyxeos administration, with a higher incidence in males compared to females. Notably, hematologic events such as febrile neutropenia and bone marrow failure were reported earlier compared to other types of adverse events.

Outcomes of adverse events

Outcomes of the reported ADRs were also analyzed. The most common outcomes were hospitalization (16.92%) and other serious medical events (59.84%) (Table 1). Death was reported in 18.33% of the cases, underscoring the severity of certain adverse events associated with Vyxeos therapy. Life-threatening events and disabilities were also reported, albeit at lower frequencies.

Discussion

The primary findings of this study indicate that Vyxeos is associated with a range of serious adverse events, with blood and lymphatic system disorders, infections, and cardiac events being the most frequently reported complications. Febrile neutropenia and sepsis were notably the most significant adverse reactions, suggesting a need for close monitoring and early intervention to manage these risks effectively.

The comparison of our findings with the existing literature provides important context. Vyxeos, a liposomal formulation of daunorubicin and cytarabine, is used in the treatment of certain hematologic malignancies but is associated with hematologic toxicities such as febrile neutropenia (FN) and

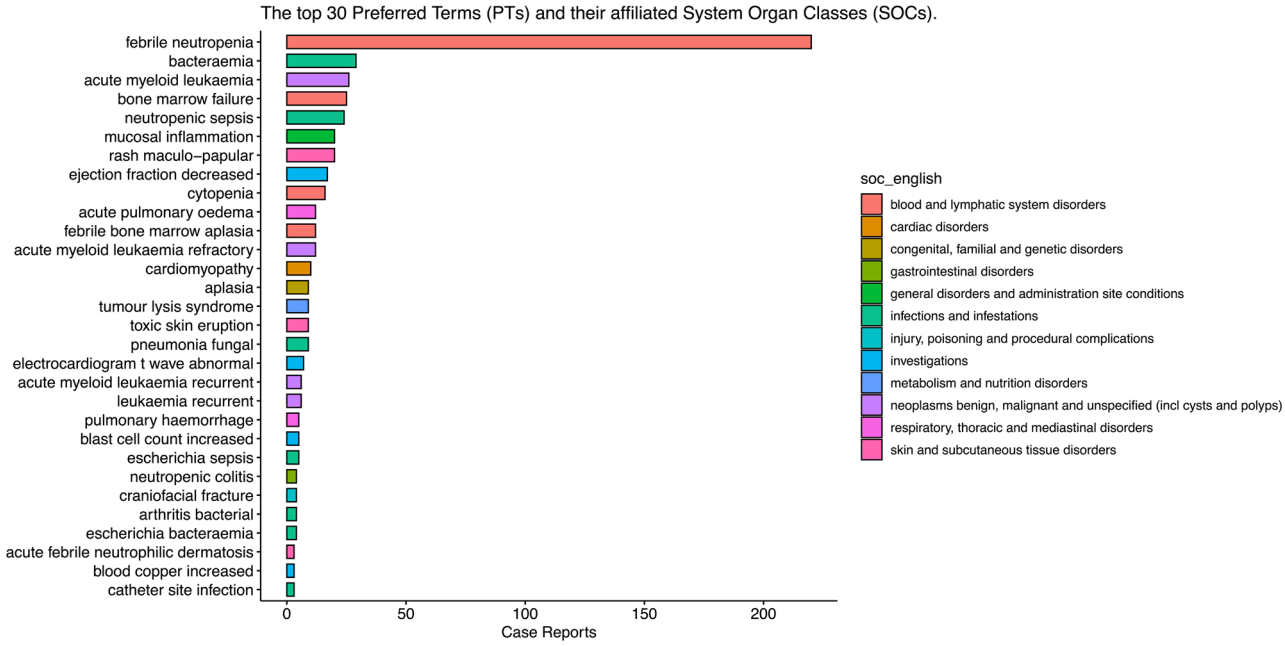

Figure 4. Top 30 preferred terms (PTs) of adverse events and their affiliated system organ classes (SOCs) reported for vyxeos. Febrile neutropenia, neutropenic sepsis, and pneumonia fungal were among the most frequently reported adverse events.

bone marrow suppression. FN is a critical condition characterized by fever and a significant reduction in neutrophil count, which can lead to severe infections and complications (Michael and Mikkael 2013; Syed and Bora 2015). Bone marrow suppression, a common side effect of chemotherapy, exacerbates the risk of FN by reducing the body's ability to produce white blood cells (Singh et al. 2022). The high incidence of FN observed in Vyxeos-treated patients aligns with previous clinical studies, emphasizing the need for proactive management strategies. Prophylactic measures such as granulocyte colony-stimulating factors (G-CSF), antibiotics, and growth factors are essential to reduce FN-related mortality (Gonçalo et al. 2015). Prompt initiation of empirical antibiotics is critical, and empirical antifungal therapy is recommended for high-risk patients with persistent fever despite antibacterial treatment (Sharma and Lokeshwar 2005). However, our study did not stratify data specifically by disease subtype (therapy-related AML versus MDS-related AML), which may influence the incidence and severity of FN. Further research is needed to examine the differences in FN incidence and severity between these subtypes, as this could provide valuable insights into disease-specific toxicities. While Vyxeos is effective in treating certain leukemias, its hematologic toxicities necessitate careful management to mitigate risks. Proactive interventions can significantly improve patient outcomes, but the psychosocial and financial burdens of FN, along with potential chemotherapy dose adjustments, highlight the complexity of managing these toxicities (Jean 2014).

Infections, particularly neutropenic sepsis and fungal pneumonia, were another major category of adverse events. Vyxeos, a liposomal formulation of daunorubicin and cytarabine, is used in the treatment of acute myeloid leukemia (AML) and is associated with a high risk of infections, especially in neutropenic patients. Neutropenic sepsis and fungal pneumonia are significant complications in this context. Invasive fungal infections (IFIs) are prevalent in neutropenic patients, with Candida and Aspergillus being the most common pathogens, accounting for approximately 50% and 40% of cases, respectively (Gea-Banacloche et al. 2003). The incidence of fungal infections in neutropenic patients with hematologic malignancies is high, with a mortality rate of 64% for fungal pneumonia, particularly for zygomycosis (Ayesha et al. 2014). The diagnosis of fungal infections in neutropenic patients is challenging due to nonspecific symptoms and the need for early intervention. Clinical features such as persistent fever in neutropenic patients often necessitate empirical antifungal therapy (Gea-Banacloche et al. 2003). Radiological patterns, such as lung nodules, can provide clues to the type of fungal infection (Ayesha et al. 2014). Prophylaxis and treatment of IFIs in neutropenic patients are guided by evidence-based recommendations, such as those from the European Conference on Infections in Leukemia (ECIL-3) (Agnieszka and Agnieszka 2011). Echinocandins and voriconazole are commonly used antifungal agents, with voriconazole being effective against Aspergillus infections (Thomas and Maria 2013). However, the emergence of resistant fungal pathogens, such as triazole-resistant Candida and echinocandin-resistant species, poses a significant challenge and underscores the need for new antifungal strategies (Thomas and Maria 2013). These findings underscore the importance of infection prophylaxis, including the use of broad-spectrum antibiotics and antifungal agents, in patients receiving Vyxeos, particularly during the period of profound neutropenia. The management of these infections requires a comprehensive understanding of the epidemiology, diagnosis, and treatment strategies for IFIs to improve patient outcomes.

Cardiac events, including arrhythmia and pericarditis, were observed more frequently in female patients. This observation is consistent with prior studies on anthracycline-based

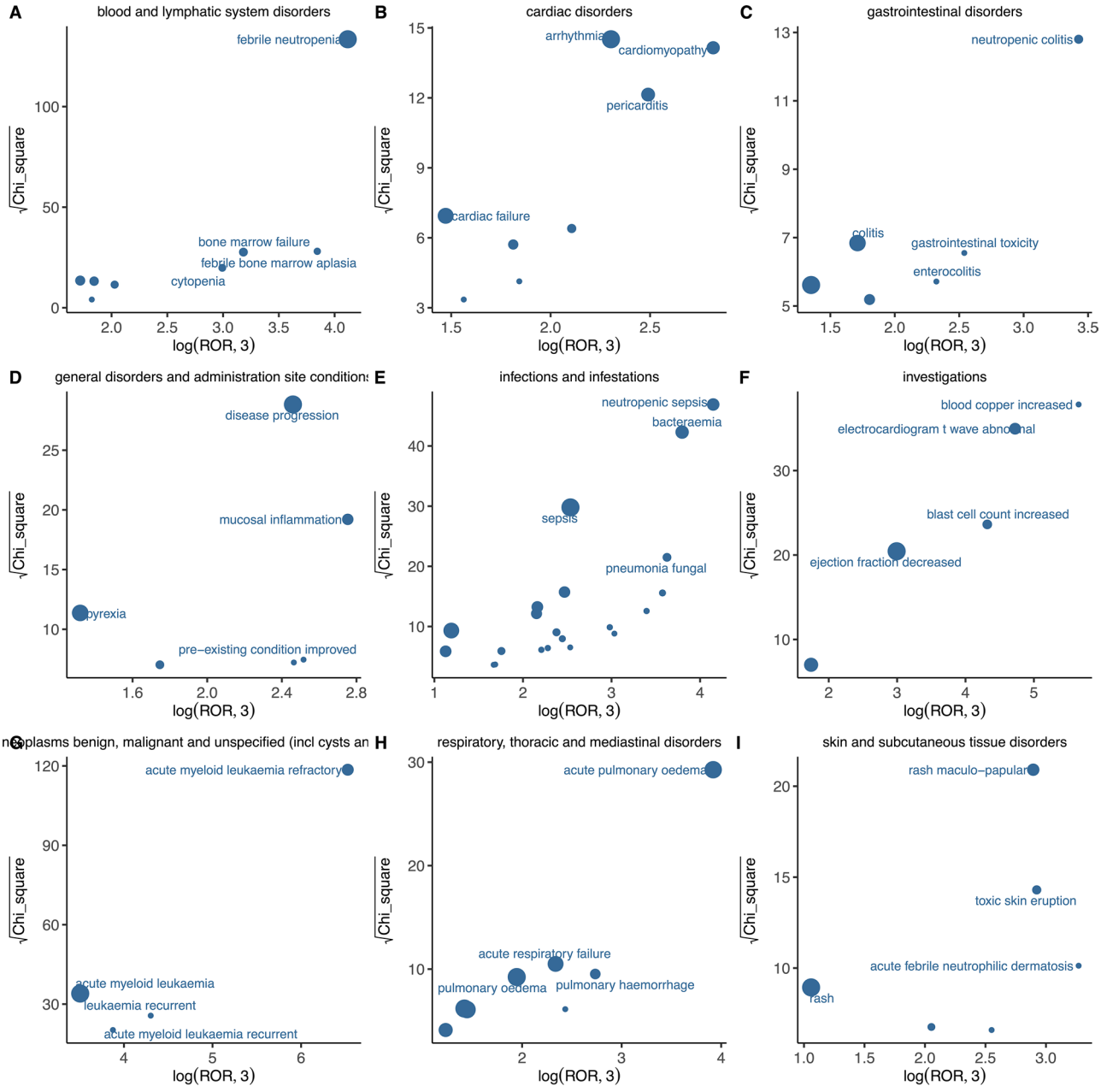

Figure 5. Logarithmic representation of Reporting Odds ratios (ROR) for different adverse events linked to vyxeos.
The figure provides a comparative overview of hematologic, cardiac, gastrointestinal, and infection-related events, with febrile neutropenia showing the highest association.

therapies, which have reported a risk of cardiotoxicity. While the provided studies do not directly address Vyxeos, they offer insights into cardiac events such as arrhythmias and pericarditis, which are relevant to understanding potential side effects of treatments like Vyxeos (Peter et al. 2009; Panos et al. 2015; Boyadzhieva et al. 2023). Cardiac arrhythmias, particularly atrial fibrillation, are significant concerns in patients undergoing treatment for hematologic conditions, as they can impact overall treatment outcomes and patient safety. Vagus nerve stimulation (VNS) has also been linked to late-onset cardiac arrhythmias, suggesting that external factors, such as medical devices, may influence cardiac health (Peter et al. 2009). Although liposomal formulations aim to reduce off-target effects, our findings suggest that cardiac monitoring remains essential, especially in patients with preexisting cardiovascular conditions and those at risk of systemic inflammatory complications.

Geographic variability in adverse event reporting was also observed, with the United Kingdom and the United States contributing the highest number of reports. This could be attributed to differences in healthcare systems, patient demographics, or pharmacovigilance practices. Relying on data primarily from these regions may limit the generalizability of findings, as it may not fully capture the diversity of patient populations globally. To enhance the global applicability of drug safety monitoring, future studies should aim to include broader datasets from underrepresented regions, such as Asia, Africa, and Latin America. Standardized approaches to adverse event reporting across regions are necessary to ensure that drug safety is consistently monitored worldwide.

Table 4. Subgroup analysis of signal strength of reports of female at the preferred term level in the FAERS database.

Soc	pt	Case reports	ROR(95% CI)	PRR(95% CI)	Chisq	IC(IC025)	EBGM(EBGM05)
Infections and infestations	Neutropenic sepsis	5	82.66(34.24, 199.52)	82.11(33.99, 198.36)	399.1	6.35(5.19)	81.8(39.13)
	Bacteremia	10	95.37(51.03, 178.25)	94.09(51.25, 172.75)	917.15	6.55(5.69)	93.69(55.52)
	Sepsis	22	21.9(14.33, 33.48)	21.28(14.1, 32.12)	425.36	4.41(3.81)	21.26(14.9)
	Septic shock	4	10.37(3.88, 27.71)	10.32(3.87, 27.5)	33.66	3.37(2.1)	10.31(4.53)
	Device related infection	4	26.25(9.82, 70.16)	26.11(9.8, 69.57)	96.5	4.7(3.44)	26.08(11.45)
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	6	29.41(13.16, 65.7)	29.17(13.06, 65.15)	163.08	4.86(3.79)	29.14(14.87)
	Pleural effusion	6	9.99(4.47, 22.32)	9.92(4.44, 22.16)	48.15	3.31(2.24)	9.92(5.06)
Blood and lymphatic system disorders	Febrile neutropenia	73	134.41(105.49, 171.25)	121.21(97.7, 150.37)	8661.19	6.91(6.57)	120.54(98.42)
	Bone marrow failure	7	32.31(15.34, 68.05)	32.01(15.2, 67.41)	210.06	5(3.99)	31.97(17.14)
	Cytopenia	5	37.16(15.41, 89.61)	36.92(15.28, 89.19)	174.44	5.2(4.04)	36.85(17.64)
	Febrile bone marrow aplasia	3	70.12(22.52, 218.31)	69.83(22.4, 217.64)	202.9	6.12(4.7)	69.61(26.91)
	Pancytopenia	9	16.91(8.76, 32.64)	16.72(8.76, 31.93)	132.97	4.06(3.16)	16.7(9.63)
	Thrombocytopenia	11	11.1(6.12, 20.13)	10.95(6.08, 19.71)	99.51	3.45(2.63)	10.94(6.65)
Cardiac disorders	Pericarditis	3	11.34(3.65, 35.27)	11.3(3.63, 35.22)	28.17	3.5(2.08)	11.3(4.37)
	Arrhythmia	7	15.38(7.3, 32.38)	15.24(7.24, 32.1)	93.14	3.93(2.92)	15.23(8.17)
	Cardiomyopathy	7	58.76(27.88, 123.81)	58.21(27.64, 122.59)	392.58	5.86(4.85)	58.05(31.12)
	Myocarditis	3	28.03(9.01, 87.18)	27.92(8.96, 87.02)	77.78	4.8(3.38)	27.89(10.79)
	Pericardial effusion	3	12.11(3.89, 37.64)	12.06(3.87, 37.59)	30.43	3.59(2.17)	12.06(4.67)
General disorders and administration site conditions	Mucosal inflammation	5	18.56(7.7, 44.75)	18.44(7.63, 44.55)	82.46	4.2(3.04)	18.43(8.83)
	Disease progression	20	17.57(11.26, 27.4)	17.12(11.12, 26.35)	303.74	4.1(3.47)	17.1(11.79)
	Preexisting condition improved	4	40.85(15.27, 109.22)	40.63(15.25, 108.26)	154.34	5.34(4.07)	40.55(17.81)
	Multiple organ dysfunction syndrome	4	11.81(4.42, 31.55)	11.75(4.41, 31.31)	39.33	3.55(2.28)	11.74(5.16)
Gastrointestinal disorders	Gastritis	3	9.85(3.17, 30.61)	9.81(3.15, 30.58)	23.74	3.29(1.88)	9.81(3.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukemia	7	53.42(25.35, 112.55)	52.92(25.13, 111.45)	355.75	5.72(4.72)	52.79(28.3)
Investigations	Electrocardiogram qt prolonged	6	13.43(6.01, 30.01)	13.33(5.97, 29.77)	68.45	3.74(2.66)	13.33(6.8)
	Ejection fraction decreased	7	43.3(20.56, 91.22)	42.9(20.37, 90.35)	285.96	5.42(4.41)	42.82(22.95)
	Electrocardiogram t wave abnormal	5	385.87(158.89, 937.09)	383.26(158.65, 925.85)	1872.9	8.56(7.39)	376.55(179.22)
Skin and subcutaneous tissue disorders	Rash maculo-papular	3	12.81(4.12, 39.82)	12.76(4.09, 39.77)	32.51	3.67(2.25)	12.75(4.94)
Nervous system disorders	hemorrhage intracranial	4	40.29(15.07, 107.74)	40.08(15.04, 106.79)	152.15	5.32(4.05)	40.01(17.57)
	Cerebral hemorrhage	4	13.64(5.1, 36.44)	13.57(5.09, 36.16)	46.55	3.76(2.49)	13.56(5.96)

This study has several strengths, including the use of a large, publicly available dataset that provides real-world evidence of Vyxeos safety. The comprehensive analysis of adverse events and the inclusion of various disproportionality metrics strengthen the reliability of our findings. However, the study also has limitations. The reliance on spontaneous reporting data, which is inherently prone to passive reporting and underreporting, can lead to selective reporting bias. Additionally, consumer-reported events may introduce biases, such as incomplete or inaccurate information, and there is ambiguity in determining causality between CPX-351 and reported adverse events. The lack of detailed clinical data in the FAERS database, such as comorbidities and concurrent treatments, limits the ability to analyze risk factors more comprehensively. Acknowledging these limitations helps ensure that the findings are interpreted with the appropriate level of caution and strengthens the credibility of the study. The need for standardized adverse event definitions across databases is essential for improving the accuracy and consistency of future reports.

Future research should focus on prospective studies to validate these findings and further explore the mechanisms underlying the observed adverse events. Additionally, studies evaluating the long-term safety of Vyxeos, particularly regarding cardiotoxicity and infection risks, are warranted. Furthermore, future studies should investigate potential biomarkers that could help identify patients at high risk for adverse events, thereby improving patient selection and facilitating better risk stratification.

In conclusion, Vyxeos demonstrates significant therapeutic benefits for patients with AML but is associated with a notable risk of serious adverse events, particularly hematologic and infectious complications. Healthcare professionals should remain vigilant for these potential toxicities, employing proactive measures such as infection prophylaxis and cardiac monitoring to optimize patient outcomes. Continued post-marketing surveillance and further research are essential to fully understand the safety profile of Vyxeos and improve the management of adverse events in clinical practice.

Abbreviations list

AE (Adverse Event) refers to any undesirable experience associated with the use of a medical product in a patient; BCPNN

Table 5. Subgroup analysis of signal strength of reports of male at the preferred term level in the FAERS database.

Soc	pt	Case reports	ROR(95% CI)	PRR(95% CI)	Chisq	IC(IC025)	EBGM(EBGM05)
Infections and infestations	Neutropenic sepsis	12	102.81(58, 182.22)	101.36(57.41, 178.95)	1182.13	6.65(5.86)	100.48(62.24)
	Bacteremia	9	39.69(20.56, 76.64)	39.28(20.57, 75)	334.7	5.29(4.39)	39.15(22.58)
	Sepsis	24	12.72(8.48, 19.09)	12.39(8.37, 18.34)	251.6	3.63(3.06)	12.38(8.81)
	Septic shock	6	7.22(3.24, 16.13)	7.18(3.21, 16.04)	31.93	2.84(1.77)	7.18(3.66)
	Pneumonia fungal	7	81.96(38.85, 172.92)	81.3(38.6, 171.22)	551.27	6.33(5.33)	80.73(43.22)
	Fungal infection	8	24.95(12.43, 50.09)	24.72(12.45, 49.09)	181.79	4.62(3.68)	24.67(13.77)
	Cellulitis	7	9.01(4.28, 18.96)	8.94(4.24, 18.83)	49.38	3.16(2.15)	8.94(4.79)
Respiratory, thoracic and mediastinal disorders	Acute pulmonary edema	3	40.7(13.07, 126.7)	40.56(13.01, 126.42)	115.35	5.34(3.92)	40.42(15.63)
	Pulmonary hemorrhage	3	23.62(7.59, 73.47)	23.54(7.55, 73.37)	64.62	4.55(3.14)	23.49(9.09)
	Pulmonary edema	8	11.39(5.67, 22.85)	11.29(5.69, 22.42)	75.01	3.5(2.55)	11.28(6.3)
Blood and lymphatic system disorders	Febrile neutropenia	85	72.71(58.07, 91.03)	65.51(53.85, 79.69)	5377.14	6.03(5.7)	65.14(53.98)
	Bone marrow failure	10	32.43(17.37, 60.54)	32.05(17.46, 58.84)	300.12	5(4.14)	31.97(18.96)
	Cytopenia	8	32.73(16.3, 65.72)	32.43(16.33, 64.4)	243.04	5.02(4.07)	32.34(18.04)
	Neutropenia	17	7.51(4.65, 12.14)	7.38(4.61, 11.81)	93.95	2.88(2.21)	7.38(4.93)
Cardiac disorders	Pericarditis	5	29.05(12.05, 70.06)	28.89(11.96, 69.79)	134.29	4.85(3.69)	28.82(13.8)
	Arrhythmia	13	18.79(10.86, 32.5)	18.51(10.69, 32.04)	215.2	4.21(3.45)	18.48(11.68)
General disorders and administration site conditions	Mucosal inflammation	3	7.61(2.45, 23.64)	7.58(2.43, 23.63)	17.14	2.92(1.5)	7.58(2.93)
	Disease progression	36	19.7(14.11, 27.52)	18.91(13.82, 25.88)	610.91	4.24(3.76)	18.88(14.27)
Gastrointestinal disorders	Colitis	4	6.42(2.4, 17.14)	6.39(2.4, 17.03)	18.19	2.68(1.41)	6.39(2.81)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukemia	12	46.96(26.53, 83.13)	46.31(26.23, 81.76)	530.02	5.53(4.74)	46.13(28.61)
	Acute myeloid leukemia refractory	9	2110.74(1033.57, 4310.53)	2088.32(1031.24, 4228.98)	15863.34	10.78(9.81)	1764.43(970.81)
	Acute myeloid leukemia recurrent	3	75.06(24.07, 234.08)	74.8(24, 233.14)	217.03	6.22(4.79)	74.32(28.69)
Investigations	Electrocardiogram qt prolonged	4	7.33(2.74, 19.58)	7.3(2.74, 19.45)	21.74	2.87(1.6)	7.29(3.21)
Skin and subcutaneous tissue disorders	Rash maculo-papular	8	20.51(10.22, 41.18)	20.33(10.24, 40.37)	146.84	4.34(3.39)	20.3(11.33)
	Drug eruption	3	11.09(3.57, 34.46)	11.05(3.55, 34.44)	27.4	3.46(2.05)	11.04(4.27)
Injury, poisoning and procedural complications	Craniofacial fracture	4	427.05(157.04, 1161.34)	425.04(156.43, 1154.92)	1631.2	8.68(7.38)	409.76(177.41)
	Intentional dose omission	4	8.9(3.33, 23.78)	8.86(3.33, 23.61)	27.9	3.15(1.88)	8.86(3.89)
Metabolism and nutrition disorders	Tumour lysis syndrome	5	23.62(9.8, 56.96)	23.49(9.72, 56.75)	107.47	4.55(3.39)	23.44(11.23)
Immune system disorders	Graft versus host disease	3	26.91(8.65, 83.71)	26.82(8.61, 83.59)	74.39	4.74(3.32)	26.75(10.35)
Congenital, familial and genetic disorders	Aplasia	4	89.42(33.35, 239.72)	89(33.4, 237.14)	345.36	6.46(5.19)	88.32(38.7)

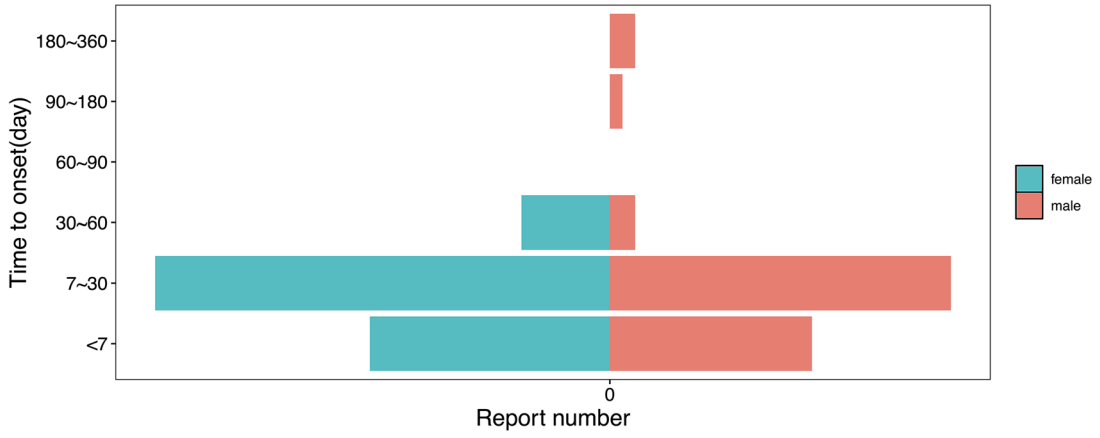

Figure 6. Time to onset of adverse events for Vyxeos-related adverse events.
The figure categorizes events by onset time ranging from less than 7 days to more than 360 days, illustrating that most adverse events occurred within the first 30 days of treatment, with differences observed between male and female patients.

(Bayesian Confidence Propagation Neural Network) is a disproportionality measure used in signal detection analysis for adverse event data; CPX-351 (Liposomal Combination of Cytarabine and Daunorubicin) is a chemotherapy drug used for the treatment of acute myeloid leukemia (AML); FAERS (FDA Adverse Event Reporting System) is a database maintained by the U.S. Food and Drug Administration (FDA) that collects and analyzes reports of adverse events associated

with drugs; MDS (Myelodysplastic Syndromes) is a group of disorders caused by poorly formed or dysfunctional blood cells; MGPS (Multi-Item Gamma Poisson Shrinker) is a disproportionality measure used in signal detection analysis for adverse event data; PRR (Proportional Reporting Ratio) is a statistical method used to evaluate the strength of association between a drug and a specific adverse event; PTs (Preferred Terms) are terms used in the MedDRA classification system to describe specific adverse events; PS (Primary Suspect) is the drug identified as the primary suspect in causing the adverse event; REAC (Reporting Entity Abbreviation Code) is a code representing the entity responsible for submitting the adverse event report; ROR (Reporting Odds Ratio) is a statistical measure used to identify the strength of the association between a specific adverse event and the drug being analyzed; SOC (System Organ Class) is a category in the MedDRA classification system used to group related adverse events by organ or system involved; t-AML (Therapy-Related Acute Myeloid Leukemia) is acute myeloid leukemia that occurs as a result of previous chemotherapy or radiation therapy; VNS (Vagus Nerve Stimulation) is a treatment method used for certain neurological conditions, which can be associated with late-onset cardiac arrhythmias.

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Author contributions

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Data availability statement

The data that support the findings of this study are available from the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS). These data are publicly accessible through the FDA's website (https://www.fda.gov/drugs/surveillance/fdas-adverse-event-reporting-system-faers). The datasets analyzed during this study were retrieved following the FAERS database's guidelines for usage, and no proprietary restrictions apply.

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