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Research Article

A Pharmacovigilance Study of the Association between Antineoplastic Agents and Neutropenia Adverse Events Based on Food and Drug Administration Adverse Event Reporting System Data

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Abstract

Neutropenia is one of the most common adverse events associated with antineoplastic agents. However, comprehensive real-world studies on the relationship between antineoplastic agents and neutropenia are relatively scarce. The objective of this study was to analyze the Adverse Events (AEs) of antineoplastic agents related to neutropenia, in order to provide a reference for the safe use of antineoplastic agents in clinical practice. We applied the Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-Item Gamma Poisson Shrinker (MGPS) models to assess the signal of antineoplastic-related adverse events due to antineoplastic agents from 2004 Q1 to 2024 Q1. The top 64 antineoplastic agents associated with neutropenia were identified. Among these, the three drugs with the highest ROR were Eribulin (ROR=45.72), Cytarabine and Daunorubicin (ROR=34.09), and Isatuximab (ROR=25.35). Excluding patients with missing sex data (11,858 patients, 14.2%), the number of female patients (40,405, 48.6%) was higher than that of male patients (31,047, 37.2%). A total of 21,135 patients (18.1%) experienced severe clinical outcomes including death or life-threatening conditions. Weibull shape parameter analysis revealed that most antineoplastic agents that cause neutropenia were characterized by early failure. Our study indicates that neutropenia should be closely monitored in the early stage of chemotherapy, and provides a reference for the rational use of antineoplastic agents in clinical practice.

Keywords: Adverse event; Antineoplastic agents; Disproportionality analysis; FAERS; Neutropenia

Introduction

In recent years, the incidence of malignant tumours has increased worldwide, and the number of new cases and deaths due to malignant tumours is among the highest in the world [1,2]. This poses a major threat to population health. Despite significant advances in scientific research and medicine, chemotherapy remains the cornerstone of most cancer treatments. It is used for patients with advanced disease when they do not respond well to local treatments, such as surgery or radiation [3,4]. Chemotherapeutic drugs have continually evolved to improve their efficacy while minimising the side effects. However, these chemotherapeutic drugs are not selective. They can inadvertently harm healthy cells, particularly those that rapidly divide. This leads to several adverse reactions, of which neutropenia is one of the most common [5-7].

Neutrophils, which typically account for 45-75 percent of all circulating white blood cells, serve as the primary defence of the immune system against foreign microorganisms. In the absence of these crucial defenders, the body struggles to combat infections, thus increasing the risk of mortality [8-10]. Chemotherapy-induced bone marrow suppression can hinder the production and maturation of neutrophils, leading to neutropenia, which refers to the condition when Absolute Neutrophil Count (ANC) in peripheral blood falls below 1.5×10^9/L [11,12]. Depending on its severity, neutropenia can be categorised into mild (ANC between 1.0×10^9/L and 1.5×10^9/L), moderate (ANC between 0.5×10^9/L and 1.0×10^9/L), and severe grades (ANC<0.5×10^9/L) [13-15]. Numerous external factors can induce neutropenia, including physical factors, infections, and medications, among which antineoplastic agents is one of the most common [16]. However, research on the link between post-market antineoplastic agents and neutropenia is limited. Therefore, analysing the relationship between antineoplastic agents and neutropenia is particularly significant.

The United States Food and Drug Adverse Event Reporting System (FAERS) is one of the most widely used databases for mining Adverse Event (AE) data. The FAERS database contains extensive data and is free and open to the public, and to some degree, reflects the occurrence of adverse drug events in the real world [17].

The objective of this study was to comprehensively evaluate the relationship between antineoplastic agents and neutropenia using real-world data from the FAERS database. Additionally, it also aimed to assess potential risk factors compare the differences between different antineoplastic agents in inducing neutropenia. The results of this study can provide a valuable reference for healthcare professionals to

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use antineoplastic drugs safely and rationally in clinical practice, so as to reduce the occurrence of adverse reactions of antineoplastic drugs.

Methods

Data Source and Processing

Data from FAERS database (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html) was downloaded from the first quarter of 2004 to the first quarter of 2024. Each ASCII data file contained seven types of data, including DEMO (personal information), DRUG (medication use records), INDI (diagnosis), OUTC (record of reported results), REAC (recording of Adverse Events), RPSR (sources of reports), THER (time of therapy). The same type of data was merged, and then deduplicated as recommended by the Food and Drug Administration (FDA) and linked according to PRIMARY-ID. The Primary Suspect drug (PS) was identified with the use of the Preferred Term (PT) "neutropenia", "febrile neutropenia", "neutropenic sepsis", "decreased neutrophil count", "decreased neutrophil percentage", "neutropenic colitis", and "neutropenic infections" from the Medical Dictionary for Regulatory Activities (MedDRA). In addition, we used the Anatomical Therapeutic Chemistry (ATC) classification of World Health Organization (https://atcddd.fhi.no/atc_ddd_index/) classifying drugs.

Signal Detection Method

Disproportionation analysis is a data-mining algorithm specifically designed to quantitatively detect ADE signals in large pharmacovigilance databases. Using the classic 2×2 contingency table, disproportionation analysis was used to compare the occurrence frequency of the target drug and target AE with the background frequency to establish a statistical association (Table 1). This study utilised statistical indicators such as the Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), multi-item gamma Poisson shrinkage (MGPS), and Bayesian Confidence Propagation Neural Network (BCPNN). The specific calculation formulas and signal statistical standards are listed in table 2. If the calculated statistical index for the target drug ADE signal exceeded these thresholds, it indicated a positive signal, suggesting a statistical relationship between the target drug and ADE, with stronger signals indicating a stronger association.

Type of Drug	N of Target Adverse Events	N of Other Adverse Events	Total
Target drug	a	b	a+b
All other drugs	c	d	c+d
Total	a+c	b+d	N=a+b+c+d

Table 1: Two-by-two contingency table for disproportionality analyses.

Algorithm	Publicity	Standard for Generating Signals
ROR	$ROR = \frac{a/c}{b/d}$	Lower 95% CI>1, N≥2
PRR	$PRR = \frac{a/(a+b)}{c/(c+d)}$ $x^2 = \sum[(O-E)^2/E]; O = a, E = (a+b)(a+c)/(a+b+c+d)$	χ2≥4, PRR≥2, N≥3
MGPS	$EBGM = \frac{a(a+b+c+d)}{(a+b)(a+c)}$	Lower 95% CI>2
BCPNN	$IC = \log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$	Lower 95% CI>0, N>0

Table 2: Overview of the main algorithms used for signal detection.

Time-to-Onset Analysis

Time to Onset (TTO) was defined as the time from the start of drug use (from START_DT in the THER file) to the occurrence of AE (from EVENT_DT in the DEMO file). We excluded reports with inaccurate data, missing data from the calculations. To assess TTO, we utilized the median, Interquartile Range (IQR), and parameters of the Weibull Distribution Shape (WSP). The shape of the Weibull distribution is determined by the scale parameter (α) and the shape parameter (β). Various types of failure patterns were analysed over time: early failures exhibit a decreasing risk of AEs over time (β<1%, 95% CI<1); random failures indicate a consistent risk of AEs over time (β close to 1, with the 95% CI containing 1); wearout failures manifest as an increasing risk of AEs over time (β>1%, with the 95% CI>1).

Statistical Analysis

Descriptive analysis was used to describe the clinical characteristics of all cases. R version 4.4.0 was used to data mining and statistical analysis.

Results

Descriptive Analysis

A total of 21,035,995 AE were reported during the study period in the FARES database. Among them, 198,907 reports of neutropenia were related to antineoplastic enrolment. The top 64 antineoplastic agents that induced neutropenia cumulatively affected 83,410 patients. The data mining process is illustrated in figure 1. The annual distribution of AE reports is shown in figure 2A, with the highest number of reports received in 2023. Healthcare professionals accounted for 52.2% (physicians constituted the largest group of submitters at 44.1 %), and the United States was the leading reporting country with 32,245 (38.7%) AE reports (Figure 2 (B & C)). This may be because most antineoplastic agents were approved for marketing in the USA. Females accounted for 48.6% and males for 37.2%, with most patients belonging to the 18-65 age group (Figure 2 (D & F)). Over 30% of the patients experienced serious AEs, and 13,561 (11.6%) patients were suspected to have died due to drug-induced neutropenia (Figure 2 (E)).

Disproportionality Analysis

After combining drug names, we identified 64 positive drugs using the four-proportion imbalance method in the FAERS database. Based on ROR, the 30 most frequently reported drugs associated with Neutropenia are listed in table 3. Of these, the top six drugs with the highest ROR were Eribulin (ROR=45.72 , N=926 cases,

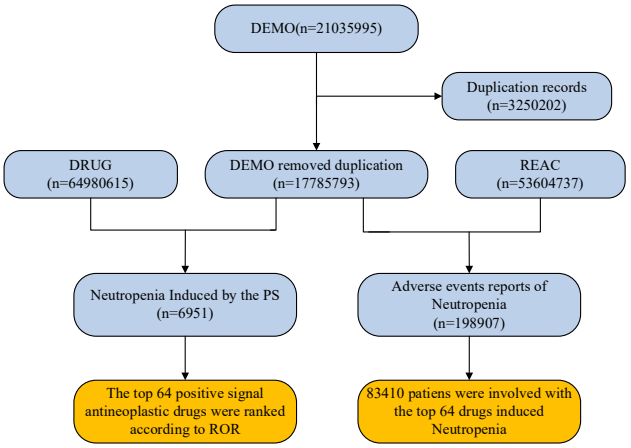

Figure 1: Flow diagram of data extraction and cleaning. (PS, primary suspect drug; ADE, adverse drug event).

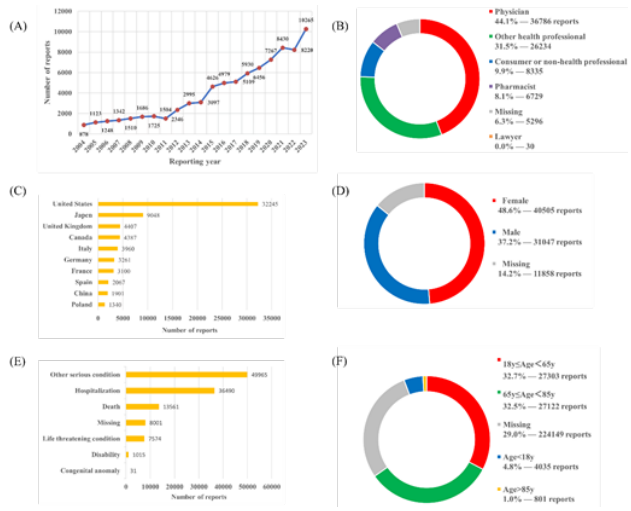

Figure 2: Basic information of adverse reaction reports related to neutropenia in the FAERS database from 2004 to 2024. (A) The number of adverse reactions was reported annually. (B) Distribution of adverse reaction reporting personnel. (C) Top 10 countries in terms of number of reported ADR cases. (D) The gender distribution of patients with adverse reactions. (E) Distribution of outcomes after occurrence of adverse effects. (F) The age distribution of patients with adverse reactions.

95% CI=42.62-49.04), Cytarabine And Daunorubicin (ROR=34.09, N=252 cases, 95% CI=29.89-38.9), Isatuximab (ROR=25.35, N=385 cases, 95% CI=22.82-28.15), Vincristine (ROR=23.98, N=1121 cases, 95%CI=22.55- 25.50), and Trabectedin (ROR=19.73, N=295 cases, 95% CI=17.52-22.21), Cytarabine (ROR=18.30, N=3254 cases, 95% CI=17.66-18.97).

Time-to-Onset Analysis

To ensure the accuracy of the TTO analysis, incorrect or missing data were excluded, resulting in fewer cases available for further analysis than initially reported. As shown in figure 3, most cases occurred within the first month after the commencement of use (n=18340, 59.98%). The cumulative distribution curve showed the onset time of neutropenia for the top six drugs, among which vincristine had the longest median onset time of 30 days (IQR: 9-102.5 days) (Figure 4).

According to the WSP assessment, all drugs except Cytarabine and Daunorubicin and Thiotepa had an upper 95% confidence interval for the shape parameter of less than 1, indicating an early failure type. Cytarabine and Daunorubicin and Thiotepa had a shape parameter of 1.46 (95% CI: 1.07 ~ 1.85) and 3.35 (95% CI: 0.31 ~ 6.39) respectively, suggesting a random failure type. Table 4 presents the TTO and WSP analysis findings for the top 30 antineoplastic agents associated with neutropenia reporting.

Discussion

Neutropenia is one of the most common adverse reactions of antineoplastic drugs. However, comprehensive studies are lacking. To the best of our knowledge, this is the first pharmacovigilance analysis of antineoplastic agents-associated neutropenia adverse events using FAERS data.

Currently, the primary mechanism by which antineoplastic agents cause neutropenia is the inhibition of and damage to functional stem cells in the bone marrow. This interference disrupts the normal maturation process of neutrophils, prevents their timely replenishment, and leads to a sharp decline in the number of mature neutrophils in the blood, ultimately resulting in neutropenia [18-20]. Additionally, neutropenia is a risk factor for infections, and cancer patients undergoing chemotherapy are prone to developing neutropenia and infections. Fever that occurs during periods of severe neutropenia is referred to as febrile neutropenia [21]. Therefore, we have chosen neutropenia, neutrophil count decreased, neutrophil percentage decreased, neutropenic infection, neutropenia sepsis, neutropenia colitis and febrile neutropenia as our target PTs.

In this study, we found that an increase in the number of events of Antineoplastic agents-induced neutropenia events starting in 2004 and peaking in 2023. We found that the proportion of neutropenia was higher in females than in males, with similar frequencies of haematologic adverse events occurring between patients aged 18-65 and those aged > 65 years. The higher number of female patients compared to male patients could be attributed to the differences in the physiological, hormonal, and genetic factors, which make women more sensitive to the side effects of chemotherapy drugs [22,23]. Owing the lack of extensive patient sex information, although the current proportion of female patients is higher than that of male patients, it is unclear whether the actual ratio of men to women using these antineoplastic agents is balanced. Moreover, about 11.6% of the patients who experience antineoplastic agents-related neutropenia died during treatment. Further investigation is warranted to study the correlation between the fatality and use of antineoplastic agents.

Moreover, we used four disproportionality analysis methods to examine the relationship between drugs and diseases. The ROR as the main criterion for assessing the correlation between antineoplastic agents and neutropenia. Our findings revealed that the six antineoplastic agents with the strongest signals were Eribulin, Cytarabine and Daunorubicin (CPX-351), Isatuximab, Vincristine, Trabectedin, and Cytarabine. The CPX-351 combination drug encapsulates cytarabine and daunorubicin in a 5:1 ratio within liposomes and is mainly used for the treatment of acute leukaemia. The traditional 7+3 chemotherapy regimen includes continuous intravenous infusion of cytarabine (100mg/m^2 per day) for 7 days, along with intravenous administration of daunorubicin (60mg/m^2) on days 1, 2, and 3. In contrast to the traditional regimen, CPX-351 offers a higher five-year survival rate, lower early mortality rate, and shorter hospital stay [24,25].

Ranking	ATC Code	Drug	Cases	ROR (95% CI)	PRR (χ^2)	EBGM(EBGM05)	IC(IC025)
1	L01XX41	Eribulin	926	45.72(42.62-49.04)	38.77(34063.92)	38.61(36.41)	5.27(3.6)
2	L01XY01	Cytarabine And Daunorubicin	252	34.09(29.89-38.9)	30.09(7107.91)	30.06(26.92)	4.91(3.24)
3	L01FC02	Isatuximab	385	25.35(22.82-28.15)	23.09(8154.23)	23.05(21.11)	4.53(2.86)
4	L01CA02	Vincristine	1121	23.98(22.55-25.50)	21.96(22402.51)	21.85(20.76)	4.45(2.78)
5	L01CX01	Trabectedin	295	19.73(17.52- 22.21)	18.35(4851.36)	18.32(16.59)	4.2(2.53)
6	L01BC01	Cytarabine	3254	18.30(17.66 - 18.97)	17.13(48866.86)	16.88(16.39)	4.08(2.41)
7	L01BC07	Azacitidine	2816	17.89(17.22 - 18.59)	16.77(41372.11)	16.56(16.04)	4.05(2.38)
8	L01AC01	Thiotepa	267	17.44(15.41 - 19.75)	16.36(3861.81)	16.34(14.73)	4.03(2.36)
9	L01FX17	Sacituzumab Govitecan	709	17.37(16.1 - 18.75)	16.3(10192.67)	16.25(15.25)	4.02(2.36)
10	L01DB01	Doxorubicin	1350	16.58(15.69 - 17.52)	15.61(18413.03)	15.51(14.81)	3.96(2.29)
11	L01CE01	Topotecan	679	15.28(14.14 - 16.52)	14.46(8512.04)	14.41(13.51)	3.85(2.18)
12	L01BB06	Clofarabine	328	15.19(13.59 - 16.98)	14.37(4090.33)	14.35(13.07)	3.84(2.18)
13	L01CB01	Etoposide	1835	14.73(14.05 - 15.45)	13.97(21994.63)	13.86(13.32)	3.79(2.13)
14	L01CA04	Vinorelbine	470	14.63(13.33 - 16.06)	13.87(5622.67)	13.84(12.8)	3.79(2.12)
15	L01FA03	Obinutuzumab	925	14.60(13.66 - 15.60)	13.84(11018.97)	13.79(13.04)	3.79(2.12)
16	L01CD04	Cabazitaxel	306	14.16(12.61 - 15.88)	13.44(3534.06)	13.43(12.19)	3.75(2.08)
17	L01EX13	Gilteritinib	411	13.51(12.24 - 14.93)	12.87(4507.87)	12.84(11.82)	3.68(2.02)
18	L01XA01	Cisplatin	2966	12.63(12.17 - 13.11)	12.07(29828.73)	11.92(11.56)	3.58(1.91)
19	L01AA03	Melphalan	279	12.51(11.09 - 14.11)	11.96(2809.05)	11.94(10.8)	3.58(1.91)
20	L01CD01	Paclitaxel	1239	12.25(11.57 - 12.97)	11.72(12129.7)	11.66(11.12)	3.54(1.88)
21	L01BB05	Fludarabine	1013	12.13(11.39 - 12.92)	11.61(9820.02)	11.56(10.97)	3.53(1.87)
22	V10XX02	Ibritumomab Tiuxetan (^{90}Y)	166	11.91(10.19 - 13.91)	11.41(1581.23)	11.4(10.01)	3.51(1.84)
23	L01AA01	Cyclophosphamide	3636	11.84(11.45 - 12.25)	11.36(33894.9)	11.18(10.87)	3.48(1.82)
24	L01BB02	Mercaptopurine	403	11.67(10.56 - 12.9)	11.19(3748.95)	11.17(10.28)	3.48(1.82)
25	L01BC02	Fluorouracil	2553	11.52(11.07 - 11.99)	11.06(23177.66)	10.94(10.58)	3.45(1.79)
26	L01FG02	Ramucirumab	300	10.90(9.71 - 12.24)	10.48(2580.17)	10.47(9.5)	3.39(1.72)
27	L01XA02	Carboplatin	5361	10.89(10.59 - 11.19)	10.48(45013.73)	10.24(10.01)	3.36(1.69)
28	L01FX05	Brentuximab Vedotin	387	10.53(9.51 - 11.66)	10.14(3195.26)	10.12(9.3)	3.34(1.67)
29	L01CE02	Irinotecan	1575	10.27(9.76 - 10.80)	9.9(12558.77)	9.83(9.43)	3.3(1.63)
30	L01AA09	Bendamustine	1012	10.12(9.50 - 10.78)	9.77(7956.57)	9.72(9.22)	3.28(1.62)

Table 3: The top 30 drugs associated with ADE of Neutropenia.

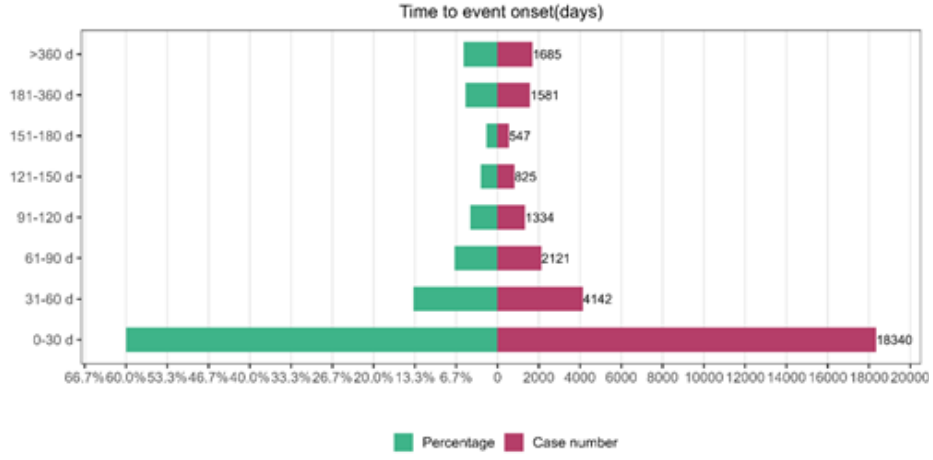

Figure 3: Time to onset of Antineoplastic-associated Neutropenia.

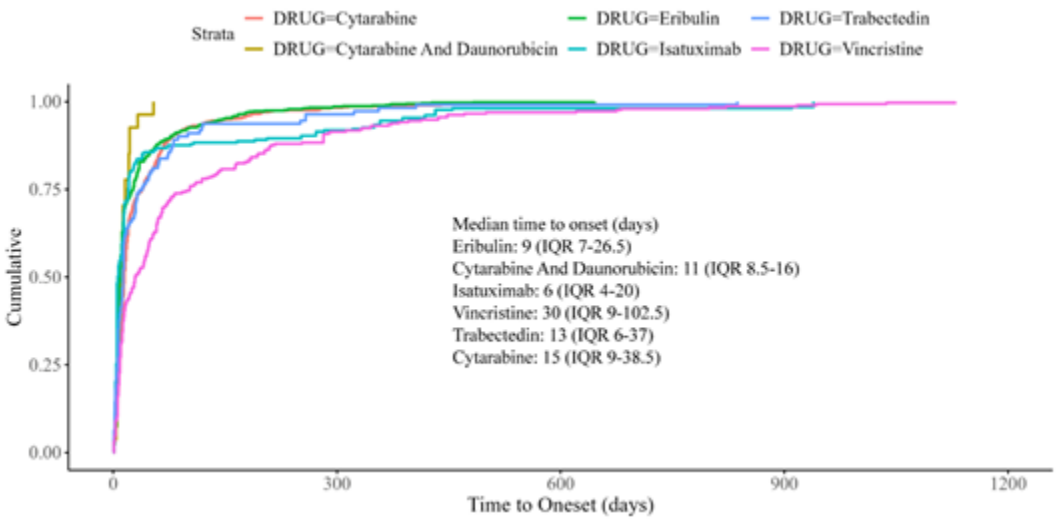

Figure 4: Cumulative curves demonstrating the onset time of top 6 antineoplastic agents-associated neutropenia adverse events after treatment with top 6 antineoplastic agents.

SN	Drug	Cases	TTO (days)		Weibull Distribution				Failure Type
				Scale Parameter		Shape Parameter			
		n	Median	IQR	α	95%CI	β	95%CI	
1	Eribulin	703	9	7-26.5	24.09	21.52-26.66	0.74	0.70-0.78	Early Failure
2	Cytarabine And Daunorubicin	27	11	8.5-16	15.27	11.11-19.44	1.46	1.07-1.85	Random Failure
3	Isatuximab	257	6	4-20	26.54	20.06-33.03	0.53	0.49-0.58	Early Failure
4	Vincristine	293	30	9-102.5	68.58	55.79-81.39	0.65	0.59-0.71	Early Failure
5	Trabectedin	111	13	6-37	30.32	21.06-39.57	0.65	0.56-0.73	Early Failure
6	Cytarabine	936	15	9-38.5	31.81	29.05-34.56	0.79	0.75-0.82	Early Failure
7	Azacitidine	1355	25	10-68	55.48	50.94-60.03	0.69	0.66-0.72	Early Failure
8	Thiotepa	4	6	5-6.25	5.86	4.09-7.64	3.35	0.31-6.39	Random Failure
9	Sacituzumab Govitecan	329	12	8-20	25.87	21.64-30.09	0.70	0.66-0.75	Early Failure
10	Doxorubicin	190	14	7.25-39.5	36.65	28.90-44.40	0.72	0.65-0.79	Early Failure
11	Topotecan	381	9	6-14	18.04	15.68-20.39	0.82	0.76-0.87	Early Failure
12	Clofarabine	190	10	6-22.75	20.21	16.35-24.07	0.79	0.71-0.87	Early Failure
13	Etoposide	343	13	9-42	29.65	25.91-33.40	0.89	0.82-0.96	Early Failure
14	Vinorelbine	161	14	8-35	30.64	24.83-36.46	0.86	0.77-0.96	Early Failure
15	Obinutuzumab	445	31	7-117	69.26	58.10-80.42	0.61	0.57-0.65	Early Failure
16	Cabazitaxel	172	7	5-18.75	21.25	16.43-26.07	0.70	0.63-0.77	Early Failure
17	Gilteritinib	168	9	4-26	20.11	15.78-24.44	0.75	0.67-0.82	Early Failure
18	Cisplatin	922	14	9-33	28.05	25.73-30.37	0.83	0.79-0.86	Early Failure
19	Melphalan	114	9	6-14.5	15.32	12.00-18.65	0.90	0.79-1.01	Early Failure
20	Paclitaxel	652	13	7-44.25	34.69	30.65-38.72	0.70	0.66-0.74	Early Failure
21	Fludarabine	285	13	6-41	35.55	27.89-43.22	0.57	0.53-0.62	Early Failure
22	Ibritumomab Tiuxetan (90Y)	122	31.5	20-46	48.45	38.23-58.67	0.89	0.79-0.99	Early Failure
23	Cyclophosphamide	1053	11	7-43	34.81	31.22-38.41	0.62	0.60-0.65	Early Failure
24	Mercaptopurine	75	35	19-104.5	109.19	68.10-150.29	0.64	0.53-0.74	Early Failure
25	Fluorouracil	962	19	11-54.75	43.75	39.91-47.58	0.77	0.73-0.80	Early Failure
26	Ramucirumab	160	10	7-19	20.69	16.71-24.67	0.86	0.77-0.95	Early Failure
27	Carboplatin	1738	14	8-39	32.25	30.22-34.27	0.80	0.77-0.82	Early Failure

28	Brentuximab Vedotin	138	7	5-15	17.53	13.44-21.62	0.76	0.67-0.85	Early Failure
29	Irinotecan	624	14	8-34	31.82	28.22-35.43	0.74	0.70-0.78	Early Failure
30	Bendamustine	415	29	7-85	51.75	43.86-59.65	0.67	0.62-0.72	Early Failure

Table 4: The TTO for the top 30 Antineoplastic agents associated with ADE of Neutropenia.

Note: CI, Confidence interval; IQR, interquartile ranges; SN, serial number; TTO, time-to-onset.

Interestingly, our study found that CPX-351 had a higher signal value than cytarabine alone but resulted in fewer cases of adverse neutropenia reactions. The reason for the less neutropenia cases with CPX-351 could be its later market approval compared to Cytarabine, resulting in less clinical data. The reason CPX-351 presents a higher risk of neutropenia than cytarabine requires further investigation.

The time interval between drug administration and the occurrence of adverse reactions is crucial for assessing drug safety as it can identify specific risk windows, thereby preventing or diagnosing adverse reactions. Our study found that most neutropenia cases induced by antineoplastic agents occurred within the first month of medication use (59.9%), followed by the second month (13.5%). Several clinical retrospective studies have shown that haematologic diseases appear within one month of chemotherapy, which is consistent with previous findings [26,27]. Research indicates that Weibull parameters can be used to describe and predict the timing of ADEs, thereby helping doctors and healthcare decision makers develop better treatment strategies and preventive measures [28,29]. In our study, we noted that most drugs causing neutropenia belonged to the early failure type. This finding suggests that neutropenia events caused by these drugs are mainly concentrated in the initial stages of medication use, and that the incidence rate of such adverse reactions shows a declining trend over time. Therefore, neutropenia should be closely monitored during the early stages of treatment. Once neutropenia is detected, the drug treatment plan can be altered or supportive measures can be implemented to help manage symptoms and prevent severe AEs.

In clinical practice, asymptomatic neutropenia often occurs during routine or occasional blood tests. Therefore, identifying and preventing the risk of developing neutropenia in patients undergoing chemotherapy is crucial. Neutropenia is a common and severe side effect of chemotherapy that not only affects patient's quality of life, but can also pose a threat to their survival. The use of preventive measures such as G-CSF (granulocyte colony-stimulating factor) medication can effectively control the occurrence of these side effects [30,31]. Regular blood monitoring and patient education are indispensable for the management of neutropenia. Through these comprehensive measures, the negative effects of chemotherapy can be significantly mitigated, thereby enhancing the safety and efficacy of the treatment.

Our study has certain advantages over recent studies. First, our findings provide a reference for the use of antineoplastic agents in clinical practice. Moreover, in addition to the ROR and PRR, we used other analytical methods (MGPS and BCPNN) that have not been used commonly in previous studies. In addition, we used the Weibull distribution to analyse the types of neutropenia caused by antineoplastic agents and summarised the relationship between antineoplastic agents and neutropenia more comprehensively.

The analysis of spontaneous reporting systems can help identify possible signals, and the FAERS is one of the largest databases. However, this study has certain limitations. First, the drug signals found by data mining were not sufficient to confirm a causal relationship between the drug and the AE. Second, the FAERS database is a self-reporting database that records real-world clinical drug use. Therefore, it may be subject to reporting bias from multiple sources and multiple confounding factors that may bias the results of the study to a certain extent. Furthermore, each report does not always contain complete information in the correct evaluation of an event and these values only provide security signals but not real risks.

Conclusion

To the best of our knowledge, this is the first pharmacovigilance analysis to examine the relationship between antineoplastic agents and the risk of neutropenia using real-world data. Our findings suggest that a complete blood cell count should be performed before the clinical use of antineoplastic agents. For patients who do not meet the treatment requirements, caution should be exercised when administering drugs, and treatment should be monitored until blood indices return to normal. Regular monitoring of blood cell counts during treatment, along with secondary prevention using prophylactic medications, is advised. Given the limitations of the database and detection methods, further long-term studies are required to validate our findings and to gain a deeper understanding of the safety profile of antineoplastic agents.

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Conflict of Interest

All the authors declare no conflicts of interest.

Author Contribution Statement

Rong Chen designed the experiment and collected the data. Lei Shi performed the analysis and wrote the paper.

References

1. Zhihao L, Chen Y, Liu D, Jiao X, Liu C, et al. (2023) The landscape of cancer research and cancer care in China. Nat Med 29: 3022-3032.

2. Wei W, Zeng H, Zheng R, Zhang S, An L, et al. (2020) Cancer registration in China and its role in cancer prevention and control. Lancet Oncol 21: 342-349.

3. Lee YT, Tan YJ, Oon CE (2023) Benzimidazole and its derivatives as cancer therapeutics: The potential role from traditional to precision medicine. Acta Pharm Sin B 13: 478-497.

4. Porras VR, Figols M, Font A, Pardina E (2023) Curcumin as a hepatoprotective agent against chemotherapy-induced liver injury. Life Sci 332: 122119.

5. Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, Hamadani M, et al. (2021) Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): A multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 22: 790-800.

6. Kanemitsu Y, Shimizu Y, Mizusawa J, Inaba Y, Hamaguchi T, et al. (2021) Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial. J Clin Oncol 39: 3789-3799.

7. Kasi PM, Grothey A (2018) Chemotherapy-induced neutropenia as a prognostic and predictive marker of outcomes in solid-tumor patients. Drugs 78: 737-745.

8. Focken J, Schittek B (2024) Crosstalk between keratinocytes and neutrophils shapes skin immunity against S. aureus infection. Front Immunol 15: 1275153.

9. Wu P, Zhang Q, Xu X, He S, Liu Z, et al. (2024) Primary infection enhances neutrophil-mediated host defense by educating HSPCs. Int Immunopharmacol 137: 112382.

10. Yang X, Ma Y, Chen X, Zhu J, Xue W, et al. (2023) Mechanisms of neutrophil extracellular trap in chronic inflammation of endothelium in atherosclerosis. Life Sci 328: 121867.

11. Family L, Li Y, Chen LH, Page JH, Klippel ZK, et al. (2018) A study of novel febrile neutropenia risk factors related to bone marrow or immune suppression, barrier function, and bacterial flora. J Natl Compr Canc Netw 16: 1201-1208.

12. Huang WC, Wu CC, Hsu YT, Chang CL (2019) Effect of hyperthermia on improving neutrophil restoration after intraperitoneal chemotherapy. Int J Hyperthermia 36: 1255-1263.

13. Dobrewa W, Bielska M, Bąbol-Pokora K, Janczar S, Młynarski W (2024) Congenital neutropenia: From lab bench to clinic bedside and back. Mutat Res Rev Mutat Res 793: 108476.

14. Matushita L, Valera ET, Aragon DC, Scridelli CA, Roxo-Junior P, et al. (2024) Chronic neutropenia in childhood: Experience of a tertiary center. J Pediatr (Rio J) 100: 311-317.

15. Palmblad J, Siersma V, Lind B, Bjerrum OW, Hasselbalch H, et al. (2020) Age-related prevalence and clinical significance of neutropenia-isolated or combined with other cytopenias: Real world data from 373 820 primary care individuals. Am J Hematol 95: 521-528.

16. Ba Y, Shi Y, Jiang W, Feng J, Cheng Y, et al. (2020) Current management of chemotherapy-induced neutropenia in adults: key points and new challenges: Committee of Neoplastic Supportive-Care (CONS), China Anti-Cancer Association Committee of Clinical Chemotherapy, China Anti-Cancer Association. Cancer Biol Med 17: 896-909.

17. Zhang Y, Fang Y, Wu J, Huang G, Bin J, et al. (2022) Pancreatic adverse events associated with immune checkpoint inhibitors: A large-scale pharmacovigilance analysis. Front Pharmacol 13: 817662.

18. Abdel-Azim H, Sun W, Wu L (2019) Strategies to generate functionally normal neutrophils to reduce infection and infection-related mortality in cancer chemotherapy. Pharmacol Ther 204: 107403.

19. Russo M, Panini N, Fabbrizio P, Formenti L, Becchetti R, et al. (2023) Chemotherapy-induced neutropenia elicits metastasis formation in mice by promoting proliferation of disseminated tumor cells. Oncoimmunology 12: 2239035.

20. Schauer T, Hojman P, Gehl J, Christensen JF (2022) Exercise training as prophylactic strategy in the management of neutropenia during chemotherapy. Br J Pharmacol 179: 2925-2937.

21. Velden WJFM, Herbers AHE, Netea MG, Blijlevens NMA (2014) Mucosal barrier injury, fever and infection in neutropenic patients with cancer: Introducing the paradigm febrile mucositis. Br J Haematol 167: 441-452.

22. Francia SD, Berchialla P, Armando T, Storto S, Allegra S, et al. (2022) Colorectal cancer chemotherapy: Can sex-specific disparities impact on drug toxicities? Eur J Clin Pharmacol 78: 1029-1038.

23. Sharifi S, Caracciolo G, Pozzi D, Digiacomo L, Swann J, et al. (2021) The role of sex as a biological variable in the efficacy and toxicity of therapeutic nanomedicine. Adv Drug Deliv Rev 174: 337-347.

24. Cortes JE, Lin TL, Asubonteng K, Faderl S, Lancet JE, et al. (2022) Efficacy and safety of CPX-351 versus 7+3 chemotherapy by European LeukemiaNet 2017 risk subgroups in older adults with newly diagnosed, high-risk/secondary AML: Post hoc analysis of a randomized, phase 3 trial. J Hematol Oncol 15: 155.

25. Muus P, Witte T (2023) CPX-351 for higher risk myelodysplastic syndrome: Cytarabine and daunorubicin in disguise? Lancet Haematol 10: 481-482.

26. Furuya Y (2019) Early neutropenia on day 8 treated with adjuvant Docetaxel-based chemotherapy in early breast cancer patients: Putative mechanisms within the neutrophil pool system. PloS One 14: 0215576.

27. Rossini D, Boccaccino A, Sbrana A, Daniel F, Borelli B, et al. (2021) Clinical impact of neutropenia and febrile neutropenia in metastatic colorectal cancer patients treated with FOLFOXIRI/bevacizumab: A pooled analysis of TRIBE and TRIBE2 studies by GONO. ESMO Open 6: 100293.

28. Mazhar F, Battini V, Gringeri M, Pozzi M, Mosini G, et al. (2021) The impact of anti-TNFα agents on weight-related changes: New insights from a real-world pharmacovigilance study using the FDA adverse event reporting system (FAERS) database. Expert Opin Biol Ther 21: 1281-1290.

29. Zou F, Cui Z, Lou S, Ou Y, Zhu C, et al. (2024) Adverse drug events associated with linezolid administration: A real-world pharmacovigilance study from 2004 to 2023 using the FAERS database. Front Pharmacol 15: 1338902.

30. Hershman DL, Bansal A, Sullivan SD, Barlow WE, Arnold KB, et al. (2023) A pragmatic cluster-randomized trial of a standing order entry intervention for colony-stimulating factor use among patients at intermediate risk for febrile neutropenia. J Clin Oncol 41: 590-598.

31. Lee S, Hong KT, Moon SJ, Choi JY, Hong CR, et al. (2022) Pharmacokinetic and pharmacodynamic characteristics of tripegfilgrastim, a pegylated G-CSF, in pediatric patients with solid tumors. Clin Pharmacol Ther 111: 293-301.

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