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Original Article

Neutropenic complications in Chinese patients with breast cancer in a real-world setting

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Abstract: Purpose: Because little is known about chemotherapy-induced neutropenic complications (CINC) in the Chinese population, this study aimed to investigate the incidence and risk factors of CINC and granulocyte colony stimulating factor (G-CSF) usage in Chinese patients with breast cancer. Methods: This study was a single-center, observational, retrospective cohort. A total of 1490 breast cancer patients who received chemotherapy from Jan 2011 to Dec 2012 were included. Multivariate logistic regression was conducted to identify the independent risk factors of CINC. Results: Without G-CSF primary prophylaxis, the CINC incidence was 46.4% in breast cancer patients. Only 1.9% of the patients received G-CSF as secondary prophylaxis, whereas 100% of the patients received G-CSF as treatment. Among the CINC patients, 29.0% received impaired chemotherapy delivery (dose reduction or delay). Risk factors for CINC were identified, such as age, neutropenia history, previous docetaxel or capecitabine treatment and abnormal baseline lymphocyte and hemoglobin levels. Present chemotherapy regimens containing paclitaxel, docetaxel, anthracycline or gemcitabine were also associated with a significantly higher risk of CINC. Conclusions: The incidence of CINC in Chinese breast cancer patients in a real-world setting was higher than generally reported. However, instead of upfront G-CSF prophylaxis, most G-CSF use in treatment was less evidence-based. The predictive risk factors for CINC was identified to guide appropriate support care and warrant the closer surveillance of patients who are at a high risk of CINC.

Keywords: Breast cancer, Chinese patients, neutropenia, risk factors

Introduction

Chemotherapy-induced neutropenia is one of the most common side effects in breast cancer patients receiving chemotherapy. Neutropenia may be complicated by fever, namely febrile neutropenia (FN), which often requires immediate hospitalization and the administration of empiric broad-spectrum antibiotics [1-3]. Such complications often lead to dose reductions or dose delays, which may affect chemotherapy delivery and compromise clinical outcomes [1, 4].

Prophylactic granulocyte colony stimulating factor (G-CSF) reduces the incidence and related infections and shortens the duration of neutropenia [5-8]. However, G-CSF is not routinely prescribed to all patients generally [9]. According to the current guidelines, the prophylactic use of G-CSF should be based on the evaluation of patients' overall risk for FN by two components: type of chemotherapy and patient-related factors. Patients can be categorized into three FN risk groups: low risk (<10%), intermediate risk (10-20%) and high risk (≥20%) [10-12]. Primary prophylactic G-CSF use is recommended by these guidelines if the patients are at a high risk of FN.

However, the risk of FN for several chemotherapy regimens is generally reported in a clinical setting, and studies have suggested that the risk of neutropenia and its complications is considerably underreported in randomized controlled trials (RCTs) [13]. Unfortunately, little is known about the actual risk of CINC for common chemotherapy regimens in the real world, in which patients' selection of procedures as RCTs could not apply generally.

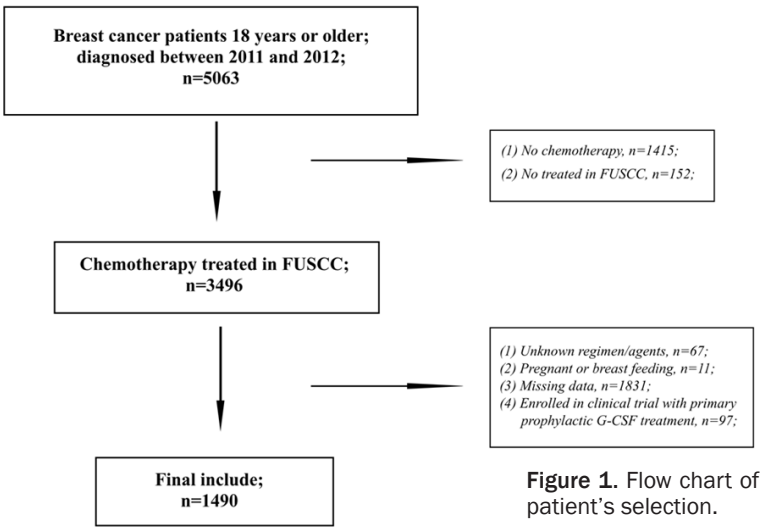

Figure 1. Flow chart of patient's selection.

In addition to the chemotherapy regimen, patient risk factors for CINC include age, performance status, nutritional status, comorbidities, chemotherapy dose intensity, previous history of neutropenia and baseline blood cell counts [14-18]. Of note, these data were mostly based on Caucasian patients. Recent studies have reported that the Chinese are more susceptible to CINC than are Caucasians in some chemotherapy regimens, such as AC (anthracycline-based chemotherapy containing doxorubicin and cyclophosphamide) and TC (docetaxel and cyclophosphamide) [9, 19, 20]. These results suggest that Chinese patients are more vulnerable to suffering from myelosuppression.

In China, no data have been published on the use of G-CSF in real-world settings. During the period of our study, due to the high cost of G-CSF, our institution, similar to most Chinese Hospitals, did not administer primary prophylactic G-CSF to breast cancer patients receiving chemotherapy, except for dose-dense regimens and interventional clinical trials. Therefore, if CINC occurred, patients were eligible for the use of G-CSF as prophylaxis only when used as secondary prevention.

The aims of this study were 1) to investigate the incidence and risk factors of CINC in Chinese patients with breast cancer in a real-world setting and 2) to provide recent data on the patterns of CSF use in daily practice.

Methods

Design and setting

This was a single-center, retrospective, observational study conducted at Fudan University Shanghai Cancer Center (FUSCC), which is one of the largest and leading cancer centers in China that treats approximately 20,000 breast cancer cases annually. Data were extracted from the institutional electronic medical record (EMR) database, and the personal information of the patients was masked.

Study population

All female patients with breast cancer who were initiated on a new chemotherapy regimen and treated at the FUSCC between January 1, 2011, and December 31, 2012, were recruited into the study. Exclusion criteria included (1) ≤18 years old; (2) pregnant or breast feeding women; (3) history of marrow or stem cell transplantation; (4) neutropenia not caused by chemotherapy; (5) had unknown cancer stage or chemotherapy agents; and (6) laboratory data not available; (7) enrolled in clinical trial with primary prophylactic G-CSF treatment.

Data collection

Data were assessed from 4 aspects: (1) patient characteristics, (2) medical history, (4) chemotherapy regimen and (4) laboratory parameters. The subsequent dose reductions and dose delays and the corresponding management were recorded for CINC.

Definitions

CINC includes severe neutropenia (absolute neutrophil count [ANC]<0.5×10^9/L) and FN (severe neutropenia and body temperature >38°C for 1 hour or >38.3°C). Dose reduction was defined as >15% reduction relative to the planned dose, and dose delay was defined as a >4-day delay in the administration of planned chemotherapy [14]. There were three patterns of G-CSF use: (1) primary G-CSF prophylaxis, if the first G-CSF claim was within 5 days of the start of the first chemotherapy cycle; (2) sec-

Table 1. Patient demographics and baseline characteristics (n=1490)

Characteristic	Mean ± standard Deviation or frequency (%)
Patient	
Age (years)	50.6 ± 9.7
Height (cm)	159.9 ± 4.7
Weight (kg)	59.4 ± 8.5
BMI (kg/m^2)	23.2 ± 3.2
BSA (m^2)	1.64 ± 0.12
Menopausal status	
Pre/peri	622 (41.7)
Post	868 (58.3)
Estrogen receptor	
Positive	889 (59.7)
Negative	601 (40.3)
Progesterone receptor	
Positive	802 (53.8)
Negative	688 (46.2)
HER-2	
Positive	436 (29.3)
Intermediate	59 (4.0)
Negative	995 (66.8)
Tumor stage	
I	241 (16.2)
II	482 (32.3)
III	211 (14.2)
IV	556 (37.3)
Bone metastasis	
Yes	276 (18.5)
No	1214 (81.5)
Past medical history	
Comorbidity	
Yes	252 (16.9)
No	1238 (83.1)
NO. of previous chemotherapy	
0	777 (52.1)
1-2	564 (37.9)
≥3	149 (10.0)
Previous chemotherapy	
Paclitaxel	167 (11.2)
Docetaxel	297 (19.9)
Nab-paclitaxel	20 (1.3)
Anthracycline	565 (37.9)
Cyclophosphamide	522 (35.0)
Gemcitabine	102 (6.8)
Capecitabine	154 (10.3)
Platinum	174 (11.7)
Vinorelbine	102 (6.8)
Fluorouracil	375 (25.2)
Previous neutropenia	
Yes	220 (14.8)
No	928 (62.3)
Unknown	342 (23.0)
Baseline laboratory parameters	
WBC (10^9/L)	6.7 ± 2.4
Lymphocyte (10^9/L)	1.6 ± 0.6
Monocyte (10^9/L)	0.4 ± 0.2
ANC (10^9/L)	4.6 ± 2.3
Hemoglobin (g/dL)	125.9 ± 13.7
Platelets (10^9/L)	235.6 ± 76.8

All values except continuous variables are expressed as percentages. Continuous variables are expressed as mean ± SD. BMI: body mass index; BSA: body surface area; WBC: white blood cell; ANC: absolute neutrophil count; Hb: haemoglobin.

ondary prophylaxis, if the first claim was within 5 days of the start of the second or subsequent cycles following the occurrence of FN or prolonged severe neutropenia; and (3) G-CSF treatment, if the first claim occurred more than 5 days after the completion of chemotherapy in any cycle [21].

Statistical analysis

Continuous variables were described as the means ± standard deviation using the Wilcoxon rank-sum test. Categorical variables were described as the number and percentage using the chi-square test or Fisher's exact test. We performed a logistic regression analysis to evaluate the association between the occurrence of CINC and covariates. Variables that were significant in the univariate analysis were included in a multivariate logistic model. A backward stepwise selection method was applied to identify independent predictors for the final model. The variables that were not statistically significant (with $P>0.05$) were removed. A two-tailed p value <0.05 was considered statistically significant, and all of the statistical analyses were performed using the software package SPSS 20.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics

A total of 1490 patients (**Figure 1**) with breast cancer were included with a mean age of 50.6

Table 2. Incidence of grade 4 neutropenia in difference chemotherapy regimen

Chemotherapy regimen[a]	N[b] (%)	G-CSF use n (%)		
		PP	SP	Treatment
Total	1490 (100%)	0	29 (1.9%)	1490 (100%)
Anthracycline-based	330 (22.1%)	0	1 (<0.1%)	330 (100%)
AC	4 (0.3%)	0	0	4 (100%)
EC	172 (11.5%)	0	1 (<0.1%)	172 (100%)
FAC	2 (0.1%)	0	0	2 (100%)
FEC	144 (9.7%)	0	0	144 (100%)
Others	8 (5.4%)	0	0	8 (100%)
Concomitant Anthracycline-Taxane Therapy	47 (3.15%)	0	2 (0.1%)	47 (100%)
Sequential Anthracycline-Taxane Therapy	242 (16.2%)	0	9 (0.6%)	242 (100%)
FEC→D	148 (9.9%)	0	5 (0.3%)	148 (100%)
EC→T	75 (5.0%)	0	0	75 (100%)
EC→D	19 (1.3%)	0	4 (0.3%)	19 (100%)
Taxane-based	681 (45.7%)	0	15 (1%)	681(100%)
Docetaxel-based	331 (22.2%)	0	15 (1%)	331 (100%)
DC	159 (10.7%)	0	10 (0.7%)	159 (100%)
D	92 (6.2%)	0	5 (0.3%)	92 (100%)
DP	40 (2.7%)	0	0	40 (100%)
DG	24 (1.6%)	0	1 (<0.1%)	24 (100%)
DX	16 (1.1%)	0	0	16 (100%)
Paclitaxel-based	349 (23.4%)	0	0	349 (100%)
TP	200 (13.4%)	0	0	200 (100%)
TG	107 (7.2%)	0	0	107 (100%)
T	42 (2.8%)	0	0	42 (100%)
Vinorelbine-based	110 (7.4%)	0	1 (<0.1%)	110 (100%)
NP	42 (2.8%)	0	0	42 (100%)
N	40 (2.7%)	0	0	40 (100%)
NX	28 (1.9%)	0	1 (<0.1%)	28 (100%)
GP	69 (4.6%)	0	0	69 (100%)
FOLFOX	12 (0.8%)	0	0	12 (100%)

[a]A: doxorubicin; C: Cyclophosphomide; D: Docetaxel; E: Epirubicin; F: Fluorouracil; G: Gemcitabine; N: Vinorelbine; P: Cisplatin, Carboplatin or Oxaliplatin; T: Paclitaxel; X: Capecitabine (Xeloda); FOLFOX: Fluorouracil, oxaliplatin, and leucovorin regimen.
[b]The regimen N values are the total number of the included patients with breast cancer. PP: primary G-CSF prophylaxis; SP: secondary G-CSF prophylaxis.

years at diagnosis from 1 January 2011 to 31 December 2012 at FUSCC. The majority of the patients were post-menopausal (58.3%), ER-positive (59.7%), PR-positive (53.8%), and stage III or IV diseased (51.5%). A total of 47.9% of the patients received previous chemotherapy, of which the most prevalent agent was anthracycline (37.9%), followed by cyclophosphamide (35.0%), fluorouracil (25.2%), and docetaxel (19.9%) (**Table 1**).

Treatment and use of G-CSF

Taxane-based regimens were the most frequently used regimens in breast cancer patients (45.7%, 23.4% with paclitaxel-based regimens and 22.2% with docetaxel-based regimens), followed by anthracycline-based (22.1%) and sequential anthracycline-taxane therapy (16.2%). Non-anthracycline and non-taxane regimens were only used in 8.2% of patients. None of the patients were treated with a dose-dense chemotherapy regimen; therefore, primary G-CSF prophylaxis was not administered. Only 29 (1.9%) of patients received G-CSF as secondary prophylaxis, whereas all (100%) patients received G-CSF as treatment when experiencing neutropenia (**Table 2**).

Table 3. Univariate analysis of CINC

Variables		CINC (n=692)	No CINC (n=798)	*P* value
Age		51.5 ± 9.5	49.9 ± 9.9	**0.002**
Height		159.7 ± 4.6	160.1 ± 4.8	0.087
Weight		58.6 ± 8.0	60.0 ± 8.9	**0.002**
BMI		23.0 ± 3.0	23.4 ± 3.3	**0.010**
BSA		1.63 ± 0.12	1.65 ± 0.13	**0.005**
Menopausal status	Pre/peri	273	349	0.094
	Post	419	449	
Tumor stage	I	114	127	0.164
	II	234	248	
	III	106	105	
	IV	238	318	
ER	Negative	274	327	0.588
	Positive	418	471	
PR	Negative	323	365	0.717
	Positive	369	433	
HER-2	Negative	459	995	0.890
	Positive	204	436	
	Intermediate	29	59	
Bone metastasis	No	569	645	0.488
	Yes	123	276	
Comorbidity	No	577	662	0.827
	Yes	115	136	
NO. of previous chemotherapy				
	0	346	431	**0.006**
	1-2	289	275	
	≥3	57	92	
Recent surgery	No	394	480	0.209
	Yes	298	318	
Previous chemotherapy				
Paclitaxel	No	613	710	0.813
	Yes	79	88	
Docetaxel	No	587	606	**<0.001**
	Yes	105	192	
Nab-paclitaxel	No	687	783	0.053
	Yes	5	15	
Anthracyclines	No	416	509	0.145
	Yes	276	289	
Cyclophosphamide	No	427	541	**0.014**
	Yes	265	257	
Gemcitabine	No	649	739	0.369
	Yes	43	59	
Capecitabine	No	649	739	**<0.001**
	Yes	43	59	
Platinum	No	612	704	0.896
	Yes	80	94	
Vinorelbine	No	646	742	0.778

Incidence of CINC

In the 1490 patients without primary G-CSF prophylaxis, 692 (46.0%) patients developed CINC, of which 496 cases (33.3%) occurred in the first cycle. The three chemotherapy regimens that were associated with a high risk of CINC used in breast cancer were docetaxel-based (72.5%), sequential anthracycline-taxane therapy (52.1%), and anthracycline-based (48.5%).

Impact of CINC on chemotherapy administration

Among the 692 patients who developed CINC, 104 (15.0%) experienced dose reductions, 82 (11.8%) experienced dose delays, and 15 (2.2%) experienced regimen discontinuation. Overall, 201 (29.0%) of patients developing CINC experienced at least one of the above-mentioned impairments upon their chemotherapy delivery.

Risk factors of CINC

In a univariate analysis, we explored all of the candidate predictors for CINC in any cycle of chemotherapy. Patient-related factors that were significantly associated with CINC were age, BMI (body mass index), BSA (body surface area), previous chemotherapy and neutropenia history. In addition, the laboratory parameters, abnormal WBC (white blood cell counts); monocyte, ANC and hemoglobin levels influenced the occurrence of CINC (**Table 3**).

In the multivariate analysis, we carried out a stepwise

	Yes	46	56	
Fluorouracil	No	484	631	**<0.001**
	Yes	208	167	
Pre-existing neutropenia	No	414	514	**<0.001**
	Yes	127	93	
	Unknown[a]	151	191	
Present chemotherapy				
Paclitaxel	No	631	548	**<0.001**
	Yes	61	250	
Docetaxel	No	358	686	**<0.001**
	Yes	334	112	
Nab-paclitaxel	No	663	744	**0.031**
	Yes	29	54	
Anthracyclines	No	461	522	0.624
	Yes	231	276	
Cyclophosphamide	No	368	506	**<0.001**
	Yes	324	292	
Monoclonal antibody	No	615	721	0.350
	Yes	77	77	
Gemcitabine	No	644	650	**<0.001**
	Yes	48	148	
Capecitabine	No	669	776	0.524
	Yes	23	22	
Platinum	No	582	554	**<0.001**
	Yes	110	244	
Vinorelbine	No	645	722	0.056
	Yes	47	76	
Fluorouracil	No	589	678	0.934
	Yes	103	120	
WBC	Normal	601	717	0.051
	Abnormal	91	79	
Lymphocyte	Normal	641	76**0**	**0.03**5
	Abnormal	51	3**8**	
Monocyte	Normal	651	771	**0.009**
	Abnormal	41	25	
ANC	Normal	605	731	**0.005**
	Abnormal	87	65	
Hb	Normal	589	705	**0.049**
	Abnormal	103	91	
Platelet	Normal	563	650	0.981
	Abnormal	129	148	

[a]Missing category introduced to avoid loss of observations. BMI: body mass index; BSA: body surface area; WBC: white blood cell; ANC, absolute neutrophil count; Hb: haemoglobin.

logistic regression with backward selection. The independent predictors of CINC were older age (OR=1.02; 95% CI: 1.00-1.03; *P*=0.016), neutropenia history (OR=2.52; 95% CI: 1.64-3.86; *P*<0.001), previous docetaxel treatment (OR=0.61; 95% CI: 0.42-0.89; *P*=0.011), previous capecitabine treatment (OR=0.54; 95% CI: 0.35-0.85; *P*=0.007), abnormal lymphocyte level (OR=1.33; 95% CI: 1.03-1.72; *P*=0.030), abnormal hemoglobin level (OR=1.24; 95% CI: 1.04-1.48; *P*=0.018), present paclitaxel treatment (OR=0.49; 95% CI: 0.34-0.72; *P*<0.001), present docetaxel treatment (OR=5.13; 95% CI: 3.58-7.35; *P*<0.001), present anthracycline treatment (OR=1.75; 95% CI: 1.20-2.54; *P*=0.003), and present gemcitabine treatment (OR=0.53; 95% CI: 0.35-0.80; *P*=0.003) (**Table 4**).

Discussion

This study is the first to evaluate the incidence, risk factors and management of CINC in Chinese clinical practice.

The incidence of CINC for the investigated regimen was 46.0%, which is much higher than previously reported (10%-34%) [18, 22, 23]. One possible reason is that all of the reported risks were generally obtained from RCTs [13], but we analyzed unselected patients in a real-world setting. Different from RCTs, patients in real-world clinical practice may have a higher CINC risk due to older age, poorer performance status, and severe comorbidities [24-26]. Another possible reason is ethnicity. CYP3A enzymes play an important role in the metabolism of docetaxel [27]. However, the Chinese population has lower CYP3A activity than do other races [28, 29]. This poor clearance may result in the accumulation of docetaxel, and the risk of myelosuppression may thus demonstrate a corresponding increase. In our

Table 4. Multivariate analysis of CINC

Variables	Odds Ratio	95% CI	*P* value
Age	1.02	1.00-1.03	0.016
Previous docetaxel treament	0.61	0.42-0.89	0.011
Previous capecitabine treatment	0.54	0.35-0.85	0.007
Pre-existing neutropenia[a]			<0.001
Yes	2.52	1.64-3.86	<0.001
Unknown	1.85	1.28-2.68	0.001
Present paclitaxel treatment	0.49	0.34-0.72	<0.001
Present docetaxel treatment	5.13	3.58-7.35	<0.001
Present anthracyclines treatment	1.75	1.20-2.54	0.003
Present gemcitabine treatment	0.53	0.35-0.80	0.003
Abnormal lymphocyte level	1.33	1.03-1.72	0.030
Abnormal Hb level	1.24	1.04-1.48	0.018

[a]Reference category: No pre-existing neutropenia: OR, 1.00; CI: confidence interval; Hb: haemoglobin.

study, 331 patients received docetaxel-based regimens, and more than 70% of them experienced CINC.

Similar to previous studies, several risk factors were identified as being associated with higher CINC risk, including older age, neutropenia history, and abnormal lymphocyte and hemoglobin levels [14, 16, 22, 30, 31]. Chinese patients received a variety of chemotherapy regimens for treating their breast cancer in daily clinical practice, which made it difficult to evaluate the risk factors for CINC by focusing on a particular chemotherapy regimen, such as TC or FEC [19, 30]. According to the treatment characteristics described by Lyman et al [32], we also assessed risk factors of CINC associated with a single chemotherapy agent. The results show that present chemotherapy regimens containing docetaxel, anthracycline, paclitaxel or gemcitabine were significantly associated with a higher risk of CINC. In particular, the patients who received docetaxel were nearly 5 times more likely to develop CINC than were those who received other agents. Although receiving anthracycline was not significant in the univariate analysis, it was used in the multivariate analysis due to the higher risk of CINC (25%) in the AC chemotherapy regimen in Chinese patients [9]. The results show that anthracycline became a strong predictor in the final model for interacting with other variables. Moreover, previously receiving docetaxel or capecitabine was found to be a protective factor of CINC, which is a new finding. Although the reason for these findings is not clear from our analysis, it may indicate that these patients used less aggressive chemotherapy regimens in the present treatment.

In contrast to other studies, comorbidities such as diabetes and hypertension were not associated with a higher risk of CINC in our study. The percentage of patients presenting at least one comorbidity was 17.0%, which was much lower than that previously reported, with values of 39.0%-50.8% [33, 34]. Part of this difference is explained by China's age-specific incidence. The mean age at diagnosis of breast cancer in China is 45-55 years, which is younger than that for Western women [35]. In 2008, 16.6% of patients with breast cancer were aged ≥65 years in China (compared with 42.6% of patients in the USA) [36]. Only 89 (6.0%) patients were aged >65 years in our study, which could be attributed to a lower comorbidity incidence in younger women.

In our study, the high proportion of CINC had a significant impact on chemotherapy delivery. Approximately 30.0% of the patients who developed CINC experienced dose reductions, dose delays and regimen discontinuation in the following cycles. Dose reductions and delays led directly to lower RDI (Relative Dose Intense) (≤85%) achievement in routine practice and, consequently, lower survival [37-39]. Many studies have shown that primary prophylactic G-CSF is associated with higher RDI. Current guidelines suggest the consideration of G-CSF prophylaxis not only when the FN risk is ≥20% but also to maintain planned dose delivery. However, without using dose-dense regimens, none of the patients received primary G-CSF prophylaxis; secondary prophylaxis was used in only 1.9% of patients due to CINC in this study. Compared with prophylaxis, there is less evidence supporting the therapeutic use of G-CSF. Patients with severe neutropenia are not considered to benefit from G-CSF treatment in the current guidelines. Routine G-CSF treatment in non-febrile patients with severe neutropenia can reduce the duration of neutropenia but does not affect the clinical outcome [10-12]. For patients with FN, these guidelines do not

recommend the routine addition of G-CSF to antibiotics for the treatment of FN, although the guidelines do state that G-CSF should be considered in patients with risk factors for infection-related complications. Regardless of these recommendations, in this study, nearly all of the patients (100%) received G-CSF for treatment after a neutropenia episode (ANC< 2.0×10^9/L). A recent study also showed that 96% of G-CSFs were administered in scenarios where G-CSF therapy is not recommended by evidence-based guidelines [40]. These findings suggest a largely higher discretionary use of G-CSF in general clinical practice.

There are also limitations in our study. As a retrospective study, some information on EMR could be unavailable, such as ECOG performance and dose, which are well-established risk factors for neutropenia in many studies [32, 41-44]. Moreover, the collection of the evaluated data from our single center limited the model's general application.

Despite these limitations, our study has several important strengths. First, our study is based on a large adult population with breast cancer (n=1490). Second, the collected data are not confined to any specific cancer stage or chemotherapy type. Third, we also provide real-world data on the incidence of CINC and patterns for G-CSF use in China.

In conclusion, we identified the incidence and risk factors of CINC in Chinese breast cancer patients receiving common chemotherapy regimens. Understanding the types of patients at risk for these complications is essential to improve monitoring and counseling and to provide future targeted prophylaxis measures for adherence to guidelines.

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Disclosure of conflict of interest

None.

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