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Incidence of Chemotherapy-induced Severe Neutropenia in Nadir Period in Gynecologic Cancer Patients Receiving Carboplatin and Paclitaxel

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ABSTRACT

Objectives: This study aimed to determine the incidence of chemotherapy-induced severe neutropenia in the nadir period among gynecologic cancer patients receiving carboplatin and paclitaxel.

Materials and Methods: This prospective cohort study recruited 150 gynecologic cancer patients receiving carboplatin and paclitaxel. Complete blood counts were collected before receiving chemotherapy and during the nadir period of each cycle, followed until discontinuation of the regimen or completion of six cycles, to evaluate the incidence of severe neutropenia.

Results: A total of 793 cycles were analyzed in 150 patients. Severe neutropenia occurred in 366 cycles and 111 patients during the nadir periods, with 46.2% per cycle and 74.0% per patient, respectively. The incidence tended to increase in later cycles. The prior use of granulocyte-colony stimulating factor was 2.9%. The incidence of febrile neutropenia was 4.7%. No additional treatment for severe neutropenia was provided in 80.2%. Postmenopausal status and an initial white blood cell count below 7,000 cells/μL were significant risk factors for severe neutropenia. Additionally, an initial absolute neutrophil count (ANC) below 5,000 cells/μL was a significant risk factor for febrile neutropenia.

Conclusion: Despite severe neutropenia being relatively common during the nadir periods, the majority did not receive further management and subsequently recovered. Furthermore, the incidence of febrile neutropenia was low. Therefore, evaluation of ANC in nadir periods should be selectively performed in patients at risk for severe and febrile neutropenia.

Keywords: chemotherapy-induced neutropenia, nadir, gynecologic cancer, Carboplatin, Paclitaxel.

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อุบัติการณ์การลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรง ในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาว ในผู้ป่วยมะเร็งทางนรีเวชที่ได้รับยาเคมีบำบัดสูตร Carboplatin และ Paclitaxel

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บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาอุบัติการณ์การลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรง ในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาว ในผู้ป่วยมะเร็งทางนรีเวชที่ได้รับยาเคมีบำบัดสูตร Carboplatin และ Paclitaxel*

วัสดุและวิธีการ: *การศึกษาไปข้างหน้า ด้วยการเก็บข้อมูลผู้ป่วยจำนวน 150 คน ที่วินิจฉัยเป็นมะเร็งนรีเวชและได้รับยาเคมีบำบัดสูตร Carboplatin และ Paclitaxel โดยเก็บข้อมูลผลเลือดการตรวจความสมบูรณ์ของเม็ดเลือด ก่อนให้ยาเคมีบำบัดและในสัปดาห์ที่ 2 หลังการให้ยาเคมีบำบัดที่จะมีการลดต่ำสุดของเม็ดเลือดขาวในแต่ละรอบ โดยเก็บข้อมูลตั้งแต่รอบที่ 1 จนถึงรอบที่ 6 ของการให้ยาเคมีบำบัดหรือจนถึงรอบที่มีการยกเลิกการให้ยาเคมีบำบัดสูตรนี้ เพื่อศึกษาอุบัติการณ์การลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรงในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาว*

ผลการศึกษา: *จากการเก็บข้อมูลทั้งหมด 793 รอบของการให้ยาเคมีบำบัดของผู้ป่วยจำนวน 150 คน พบว่าเกิดการลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรง ในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาวจำนวน 366 รอบของการให้ยาเคมีบำบัด และเกิดใน 111 คนของจำนวนผู้ป่วยทั้งหมด คิดเป็นอุบัติการณ์ ร้อยละ 46.2 ของจำนวนรอบและร้อยละ 74 ของจำนวนคน โดยอุบัติการณ์มีแนวโน้มเพิ่มขึ้นในการให้เคมีบำบัดรอบถัดมา โดยมีอัตราการใช้ยากระตุ้นเม็ดเลือดขาวร้อยละ 2.9 อุบัติการณ์การเกิดภาวะไข้จากเม็ดเลือดขาวต่ำจากการลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรงร้อยละ 4.7 ในขณะเดียวกันร้อยละ 80.2 ของการเกิดภาวะเม็ดเลือดขาวชนิดนิวโทรฟิลต่ำระดับรุนแรงในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาว เม็ดเลือดขาวดีขึ้นได้เองก่อนการให้ยาครั้งถัดไปโดยไม่ต้องได้รับการรักษาเพิ่มเติม ปัจจัยเสี่ยงที่ทำให้เกิดการลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรงคือ วัยหลังหมดระดูและการที่มีเม็ดเลือดขาวก่อนให้ยาเคมีบำบัดน้อยกว่า 7,000 เซลล์ต่อลูกบาศก์เมตร ปัจจัยเสี่ยงในการเกิดภาวะไข้จากเม็ดเลือดขาวต่ำคือ การที่มีระดับเม็ดเลือดขาวชนิดนิวโทรฟิล ก่อนให้ยาเคมีบำบัดน้อยกว่า 5,000 เซลล์ต่อลูกบาศก์เมตร*

สรุป: *ถึงแม้อุบัติการณ์การลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรงในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาวในผู้ป่วยมะเร็งทางนรีเวชที่ได้รับยาเคมีบำบัดสูตร Carboplatin และ Paclitaxel จะพบได้บ่อย แต่ผู้ป่วยกลุ่มนี้ส่วนมากเม็ดเลือดขาวสามารถเพิ่มขึ้นเองได้โดยไม่ต้องได้รับการรักษาเพิ่มเติม และการเกิดภาวะไข้จากเม็ดเลือดขาวต่ำพบได้น้อย ดังนั้นการเจาะเลือดในช่วงที่มีการลดต่ำสุดของเม็ดเลือดขาวหลังได้ยาเคมีบำบัดอาจพิจารณาทำในเฉพาะผู้ป่วยที่มีความเสี่ยงต่อการเกิดการลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรงและการเกิดภาวะไข้จากเม็ดเลือดขาวต่ำ*

คำสำคัญ: *นิวโทรฟิล, ยาเคมีบำบัด, มะเร็งนรีเวช, คาร์โบพลาติน, แพ็คลิแท็กเซล*

Introduction

Gynecologic cancer is essential and common in female cancers. Among women's cancers, gynecological cancer is frequently encountered, second only to breast cancer. The most commonly encountered gynecological cancer in Thai women is cervical cancer, followed by endometrial cancer and ovarian cancer, respectively[1, 2].

Currently, gynecologic cancer treatment has undergone continuous study and development to achieve the best treatment outcomes and minimize side effects. The standard chemotherapy regimen commonly used is carboplatin/paclitaxel because of its effectiveness[3], minimal side effects[4], and flexibility for administration. This regimen is suitable for both outpatient and inpatient settings. The typical dosage includes carboplatin at an area under the concentration (AUC) versus time of 5 mg/ml/min and paclitaxel at 175 mg/m^2, administered intravenously every three weeks for at least six cycles[5]. Then, the response to chemotherapy will be examined by per vaginal examination (PV) or imaging such as ultrasound or computed tomography (CT) scan.

Carboplatin has side effects such as nausea, vomiting, nephrotoxicity, and neurotoxicity less than other chemotherapy drugs. However, it has another severe side effect: bone marrow suppression that induces neutropenia[6].

Chemotherapy-induced neutropenia has a significant impact on prognosis and overall survival. Some patients who have neutropenia will increase their risk for febrile neutropenia (FN) or secondary infections, which can lead to mortality. Therefore, detecting and treating neutropenia before severe complications are important. According to the National Cancer Institute's common terminology criteria for adverse events (CTCAE version 5.0), the severity of chemotherapy-induced neutropenia has four grades: grade 1 absolute neutrophil count (ANC): 1,500-2,000 cells/mm^3, grade 2 ANC: 1,000-1,500 cells/mm^3, grade 3 ANC: 500-1,000 cells/mm^3, and grade 4: ANC < 500 cells/mm^3. The grade 3 and 4 neutropenia are graded as severe neutropenia, requiring close monitoring for complications.

Chemotherapy-induced neutropenia often occurs 10-14 days after receiving chemotherapy (the nadir phase) and typically resolves within 21-28 days[7]. Therefore, at the Division of Gynaecologic Oncology, Faculty of Medicine, Siriraj Hospital, all patients who receive carboplatin/paclitaxel will have to be examined for the ANC to evaluate chemotherapy-induced neutropenia in the nadir phase (2 weeks after receiving chemotherapy) and before receiving the next cycle (3 weeks after receiving the last chemotherapy). Although severe neutropenia is detected during each cycle of chemotherapy, it is usually managed through subsequent monitoring before receiving the next cycle without additional treatment when there are no complications. Therefore, this study aimed to determine the incidence of chemotherapy-induced severe neutropenia at the nadir period in gynecologic cancer patients receiving carboplatin and paclitaxel at Siriraj Hospital. Additionally, the incidences of management and complication were also reported to evaluate the necessity of routinely examining the ANC in the nadir period in all patients.

Materials and Methods

This was a prospective cohort study. After approval from the Siriraj Institutional Review Board (SIRB), the patients who matched the inclusion criteria and had gynecologic cancers, including cervical cancer, corpus uteri cancer, ovarian cancer, fallopian tube cancer, and primary peritoneal cancer, and were receiving carboplatin/paclitaxel (initial dose carboplatin AUC 5 mg/ml/min/paclitaxel 175 mg/m^2) at Siriraj Hospital and could be evaluated for ANC in the nadir period and also before receiving the subsequent chemotherapy in each cycle, were recruited and informed consent had been obtained.

The researchers collected baseline blood test results, including CBC, blood urea nitrogen (BUN), creatinine, and liver function tests, before administering the first cycle of chemotherapy, as well as CBC results in the second week (nadir period) and the third week after receiving chemotherapy (before receiving the subsequent chemotherapy) of each cycle. Data has been collected from the first cycle until discontinuation of the regimen or completion of six cycles. The number of cycles that occurred in severe neutropenia and FN (complications from severe neutropenia) and the management of severe neutropenia had been collected. There was no routine use of granulocyte-colony stimulating factor (G-CSF) in this study; the use depended on the physician's decision on the severity of neutropenia. However, in all cases of febrile neutropenia, the G-CSF was used. The number of cycles using G-CSF was collected. In addition, the basic characteristics of the patients were gathered, including age, underlying disease, menopausal status, parity, Eastern Cooperative Oncology Group (ECOG) performance status scale, body mass index (BMI), episode, type, staging, and histology of cancer, history of prior surgery, radiation, and chemotherapy to evaluate the risk factors of severe neutropenia and FN. The data were recorded in case record forms.

The sample size was calculated based on the previous study of the incidence of chemotherapy-induced severe neutropenia at the nadir period in gynecologic cancer patients receiving carboplatin and paclitaxel, which was 0.29[8]. In this study, an estimation error of less than 7.5% was allowed at a 95% confidence level (type I error = 0.05, 2-sided), requiring a sample size of 140 participants. To account for 5% of data incompleteness, the total sample size for this study was 150 participants.

The data had been analyzed by the SPSS program (PASW Statistic 18) to determine, as the primary objective, the incidence of chemotherapy-induced severe neutropenia in the nadir period in gynecologic cancer patients receiving carboplatin and paclitaxel at Siriraj Hospital and reported in number, percent, and 95% confidence interval (CI). Further, the secondary objectives were evaluated: the incidence of FN, the incidence of effects on management in the next cycle of severe neutropenia in nadir periods (including no management, delayed cycle, received G-CSF, and decreased dose chemotherapy) was reported in number, percent, and 95% CI. The risk factors associated with chemotherapy-induced severe neutropenia and FN were analyzed by univariable analysis. The significant variables (p value < 0.05) from univariable analysis had been analyzed by multivariable analysis with multiple logistic regressions and backward method and were reported in odds ratio, 95% CI, and p value.

Results

During the study, there were a total of 793 cycles among 150 gynecological cancer patients receiving carboplatin and paclitaxel at Siriraj Hospital. The baseline characteristics of patients are shown in Table 1. The age ranges were 33 to 87 years. The median age was 61. 78% of the patients were in postmenopausal status. The majority of patients were ECOG 0 (76%); the others were ECOG 1 (20%), ECOG 2 (1.3%), and ECOG 3 (2%). The new case was 82%. The gynecologic cancers included cervical cancer at 8%, corpus uteri cancer at 34%, ovarian cancer, fallopian tube cancer and primary peritoneal cancer at 54%, and synchronous cancer (corpus, ovary) at 3.3%.

Table 1. Patient characteristics (Total n = 150).

Characteristics	n	%
Age		
Median 61 years (range 33-87)		
Underlying disease		
None	52	34.7
Metabolic disease	67	44.7
Other cancer	10	6.7
Other	46	30.7
Cardiac disease (IHD, VHD, AF, DCM)	6	4.0
Pulmonary disease (Asthma)	3	2.0
Thromboembolic disease (PE, DVT)	10	6.7
Renal disease (CKD)	9	6.0
Hepatic disease (Chronic HBV, Fatty liver)	2	1.3
(Chronic HBV, Fatty liver)		
Thyroid disease	6	4.0
(Hyperthyroid, Hypothyroid)		
Neurological disease	3	2.0
(Parkinson, Dementia, Alzheimer)		
Psychiatric disease	4	2.7
(MDD, OCD, schizophrenia)		
Autoimmune disease (RA, Scleroderma)	5	3.3
HIV disease	1	0.7
Genetic disease (Achondroplasia)	1	0.7
Menopause status		
Premenopausal	32	21.3
Postmenopausal	118	78.7
Parity		
0	61	40.7
≥1	89	59.3
ECOG		
0	115	76.7
1	30	20.0
2	2	1.3
3	3	2.0
BMI		
Underweight (<18.5 kg/m2)	16	10.7
Normal (18.5-22.9 kg/m2)	75	50.0
Overweight (23-24.9 kg/m2)	22	14.7
Obese (25-29.9 kg/m2)	22	14.7
Extremely obese (>30 kg/m2)	15	10.0
Episode		
New case	124	82.7
Recurrence	26	17.3

Characteristics	n	%
Cancer		
Cervix	12	8.0
Corpus	51	34.0
Ovary, Fallopian tubes, Peritoneum	82	54.7
Synchronous cancer (Corpus, Ovary)	5	3.3
Stage		
Cervix		
1		
2	52	34.7
3	67	44.7
4	10	6.7
Corpus	46	30.7
1	6	4.0
2	3	2.0
3	10	6.7
4	9	6.0
Ovary, Fallopian tubes, Peritoneum	2	1.3
1	6	4.0
2	3	2.0
3		
4	4	2.7
Synchronous cancer (Corpus, Ovary)		
1	5	3.3
2	1	0.7
3	1	0.7
Histology		
Squamous cell carcinoma	32	21.3
Adenocarcinoma	118	78.7
Other		
Disease confined in primary organ	61	40.7
No	89	59.3
Yes		
Radiation	115	76.7
No radiation	30	20.0
Before chemotherapy	2	1.3
During chemotherapy	3	2.0
Prior surgery		
No	16	10.7
Yes	75	50.0
Prior chemotherapy	22	14.7
No	22	14.7
Yes	15	10.0

IHD: ischemic heart disease, VHD: valvular heart disease, AF: atrial fibrillation, DCM: dilated cardiomyopathy, PE: pulmonary embolism, DVT: deep vein thrombosis, CKD: chronic kidney disease, HBV: hepatitis B virus, MDD: major depressive disorder, OCD: obsessive compulsive disorder, RA: Rheumatoid arthritis, HIV: Human Immunodeficiency Virus

There were 366 cycles, and 111 patients had severe neutropenia in the nadir periods. The incidence of severe neutropenia at the nadir period in gynecologic cancer patients receiving carboplatin and paclitaxel was 74% (95%CI, 66-80%) of patients and 46.15% (95%CI, 43-50%) of all cycles. 2.9% of cycles had previously used G-CSF, which could have affected the incidence. During the chemotherapy cycle, the incidence tended to rise. The incidence of severe neutropenia in each cycle is shown in Table 2.

Table 2. Incidence of severe neutropenia in nadir periods (total cycle = 793).

	n	%	95% CI	Number of prior using G-CSF		Total cycle
				n	%	
Nadir C1	45	30.00	(0.23,0.38)	2	1.33	150
Nadir C2	65	45.14	(0.37,0.53)	4	2.78	144
Nadir C3	66	48.18	(0.39,0.56)	3	2.19	137
Nadir C4	59	46.83	(0.38,0.56)	4	3.17	126
Nadir C5	68	55.74	(0.47,0.64)	6	4.92	122
Nadir C6	63	55.26	(0.46,0.64)	4	3.51	114
Total	**366**	**46.15**	**(0.43,0.50)**	**23**	**2.90**	**793**

CI: confidence interval, G-CSF: granulocyte-colony stimulating factor

The febrile neutropenia (severe neutropenia complication) was occurring in 7 patients. The incidence of febrile neutropenia from severe neutropenia was 4.7% (95%CI, 0.4-0.5%).

The effects of severe neutropenia on management in the next cycle of chemotherapy were that no additional treatment for severe neutropenia was provided at 80.2%, the delayed cycle was 13.53%, the received GCSF in the next cycle was 2.46%, and the decreased dose of chemotherapy was 1.32%. The details of management in each cycle are shown in Table 3.

Table 3. Incidence of effect to management in next cycle of severe neutropenia in nadir periods.

	No management		Delayed cycle		G-CSF		Decreased dose CMT		Total number of severe neutropenia
	n	%	n	%	n	%	n	%	
Nadir C1	35	77.78	6	13.33	2	4.44	2	4.44	45
Nadir C2	52	80.00	8	12.31	2	3.08	1	1.54	65
Nadir C3	56	84.85	5	7.58	3	4.55	0	0.00	66
Nadir C4	45	76.27	10	16.95	2	3.39	0	0.00	59
Nadir C5	55	80.88	12	17.65	0	0.00	1	1.47	68
Total	**243**	**80.20**	**41**	**13.53**	**9**	**2.46**	**4**	**1.32**	**303**

G-CSF: granulocyte-colony stimulating factor, CMT: combined modality treatment

The significant risk factors for severe neutropenia from the univariable analysis were age ≥ 50 years (OR 2.6, p = 0.038), postmenopausal status (OR 2.42, p = 0.033), initial white blood cell (WBC) below 7000 cells/ul (OR 3.88, p = 0.001), and initial ANC below 5000 cells/ul (OR 3.05, p = 0.004). The significant risk factors for severe neutropenia from multivariable analysis (multiple logistic regression, backward method) were postmenopausal status (OR 2.83, p = 0.02) and initial WBC below 7000 cells/ul (OR 4.61, p < 0.001). The significant risk factor for febrile

neutropenia from univariable and multivariable analysis was initial ANC below 5000 cells/ul (OR 2.68, p = 0.02) (Table 4).

Table 5 demonstrated the incidence of other hematotoxicity from carboplatin/ paclitaxel in the nadir period, as graded by CTCAE version 5.0.

Table 4. Risk factor for severe neutropenia and febrile neutropenia in multivariate analysis (multiple logistic regression, backward method).

	OR	95%CI	Sig. (p value)
Severe neutropenia			
Postmenopausal	2.83	1.15,6.99	0.02
WBC < 7000	4.61	1.99,10.70	< 0.001
Febrile neutropenia			
Age 70-89	3.64	0.93,14.24	0.06
ECOG 1-3	0.42	0.17,1.02	0.06
ANC < 5000	2.68	1.21,5.95	0.02

OR: odds ratio, CI: confidence interval, WBC: white blood cell count, ECOG: Eastern Cooperative Oncology Group, ANC: antenatal care

Table 5. Incidence of hematotoxicity in nadir periods (total cycles = 793).

	Grading									
	0		1		2		3		4	
	n	%	n	%	n	%	n	%	n	%
Anemia	50	6.31	347	43.76	340	42.88	55	6.94	1	0.13
Leukopenia	218	27.49	216	27.24	265	33.42	93	11.73	1	0.13
Neutropenia	182	22.95	88	11.10	157	19.80	254	32.03	112	14.12
Thrombocytopenia	766	96.60	15	1.89	6	0.76	6	0.76	0	0.00

Discussion

This study revealed that most patients (74% of patients and 46.15% of all cycles) experienced severe neutropenia in the nadir period. Although only 4.6% had the complication of severe neutropenia, FN. The use of G-CSF was 2.9%. Compared to the previous study, the incidence of severe neutropenia was in a wide range between 29-79% of patients[8-11] and 53% of the cycles[10]. The study that reported the low incidence of severe neutropenia for 29-36%[8, 9] had G-CSF support for 26%[9], and another study had the general policy of reducing the dose of chemotherapy in subsequent cycles in the presence of severe neutropenia[8]. In contrast, the study that documented the high incidence, which was approximately equal to our study for 75-79% of patients[10, 11], and 53% of the cycles[10] that administered G-CSF during the study was only 6% and did not have active management for severe neutropenia. The factors that may interfere with the incidence are the different management strategies for severe neutropenia in other studies, such as criteria for G-CSF and reduced-dose chemotherapy. The study that used more G-CSF or had an intensive policy for severe neutropenia had a lesser incidence of severe neutropenia. There was a similar incidence in the study that used G-CSF equivalent to ours. For febrile neutropenia, the incidence was low, only 1.4-6% from the prior study[8-11], and the incidence in our study was in this range. The incidence of febrile neutropenia did not appear to be impacted by the administration of G-CSF or reduced-dose chemotherapy.

The effects of severe neutropenia in the nadir period on management in the subsequence cycle of chemotherapy have not been evaluated in previous

studies. This point will be beneficial for plan management in asymptomatic severe neutropenia. In 80.2% of severe neutropenia, the ANC can improve for the next cycle of chemotherapy with no further management.

The effects of severe neutropenia in the nadir period on management in the subsequence cycle of chemotherapy have not been evaluated in previous studies. This point will be beneficial for plan management in asymptomatic severe neutropenia. In 80.2% of severe neutropenia, the ANC can improve for the next cycle of chemotherapy with no further management.

The significant risk factors for severe neutropenia in gynecologic patients receiving carboplatin/paclitaxel from multivariable analysis (multiple logistic regression, backward method) were postmenopausal status and initial WBC below 7,000 cells/ul. The significant risk factors for febrile neutropenia from the multivariable analysis were initial ANC below 5,000 cells/ul. Compared with previous studies, the significant risk factors in each study differed due to the different factors that were considered for the study and the different definitions of severe neutropenia. Some studies defined severe neutropenia as ANC less than 500/mm^3 [12, 13]; others defined it as ANC less than 1,000/mm^3 [14], similar to our study. The other significant risk factors for severe neutropenia that were similar in our study were older age (over 70 years) ($p < 0.0001$)[12]. Our study found that age ≥ 50 years and postmenopausal status were significant risk factors in univariable analysis. Although, in multivariable analysis, only postmenopausal status was the significant risk factor, it was also related to age. Our study's other significant risk factor was an initial WBC below 7,000 cells/ul, which was not the factor that previous studies considered.

For the significant risk factor of febrile neutropenia, older age was also a risk factor that has been similar in most studies. Robin et al[13] reported that the significant risk factor was age > 60 (hazard ratio 2.84; $p = 0.05$), and guidelines NCCN Clinical Practice Guidelines in Oncology 2017[15] and European Organisation for Research and Treatment of Cancer 2010[16] reported age > 65 years, in our study, older age (70-89 years) was a risk factor for febrile neutropenia (OR 3.64; $p = 0.06$), but not significant, the small sample size could be the cause.

However, preexisting neutropenia was the risk factor in our study that was compatible with the guidelines of NCCN 2017(15) and EORTC 2010[16]. Our study identified initial ANC below 5,000 cells/ul as the significant risk factor for febrile neutropenia. Although it is not within the range of neutropenia, it implies that the lower initial ANC tends to have a greater risk of febrile neutropenia.

The limitations of this study were the small sample size and the unavoidable factors that may interfere with the incidence of severe neutropenia, such as giving G-CSF or reducing the dose of chemotherapy. However, the strengths of this study were the prospective study, in which the data was almost complete and reliable, and the study of the effects of severe neutropenia in nadir on management in the next cycle of chemotherapy. No previous studies evaluated this subject, which will guide the management of asymptomatic severe neutropenia in the nadir period. Another strength was the study of various risk factors for severe neutropenia and febrile neutropenia, but due to the small sample size, some factors could not evaluate the OR.

The clinical implication of our study is the guided evaluation for ANC in nadir periods for the most safety, value, and benefit for the patients. Although severe neutropenia was relatively common during the nadir periods, the majority did not receive further management and subsequently recovered. Additionally, the incidence of febrile neutropenia was low. Thus, evaluation for ANC in nadir periods should be performed only in patients who have the risk for severe neutropenia and febrile neutropenia that are postmenopausal status, initial WBC below 7,000 cells/ul, and initial ANC below 5,000 cells/ul.

Further evaluation of the large sample size for significant risk factors for severe neutropenia and febrile neutropenia and the design for the study of the

incidence of severe neutropenia that decreased the unavoidable factor that may interfere with severe neutropenia should be considered.

Conclusion

The incidence of severe neutropenia during the nadir period in gynecologic cancer patients receiving carboplatin and paclitaxel was high, affecting 74% of patients and 46.15% of cycles, while febrile neutropenia was rare (4.7%). Most cases of severe neutropenia (80.2%) resolved without intervention. Postmenopausal status and an initial WBC < 7,000 cells/μL were significant predictors of severe neutropenia, and an initial ANC < 5,000 cells/μL predicted febrile neutropenia. These findings supported selective ANC monitoring during the nadir period for high-risk patients, optimizing resource use while maintaining patient safety.

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Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.
2. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. Int J Cancer 2021;149:778-89.
3. Akram T, Muggia FM, Fanning J. Carboplatin and paclitaxel for the treatment of advanced or recurrent endometrial cancer. Am J Obstet Gynecol 2005;192:1235-40.
4. Burke TW, Markman M, Kavanagh JJ, Morris M, Levenback C, Tornos C. Treatment of advanced or recurrent endometrial carcinoma with single-agent carboplatin. Gynecol Oncol 1993;51:255-8.
5. Markman M, Kennedy A, Webster K, Kulp B, Peterson G, Belinson J. Carboplatin plus paclitaxel in the treatment of gynecologic malignancies: The Cleveland Clinic experience. Semin Oncol 1997;24:S2-15-8.
6. Alberts DS, Hannigan EV, O'Toole R, Stock-Novack D, Anderson P, et al. Improved therapeutic index of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide: Final report by the Southwest Oncology Group of a phase III randomized trial in stages III and IV ovarian cancer. J Clin Oncol 1992;10:706-17.
7. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, et al. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 2000;18: 3038-51.
8. Markman J, Zanotti K, Webster K, Belinson J, Peterson G, Kulp B, et al. Experience with the management of neutropenia in gynecologic cancer patients receiving carboplatin-based chemotherapy. Gynecol Oncol 2004;92:592-5.
9. Pectasides D, Xiros N, Papaxoinis G, Pectasides E, Sykiotis C, Koumarianou A, et al. Carboplatin and paclitaxel in advanced or metastatic endometrial cancer. Gynecol Oncol 2008;109:250-4.
10. Guastalla JP, Pujade-Lauraine E, Weber B, Cure H, Orfeuvre H, Mousseau M, et al. Efficacy and safety of the paclitaxel and carboplatin combination in patients with previously treated advanced ovarian carcinoma: A multicenter GINECO phase II study. Ann Oncol 1998;9:37-43.
11. Miller DS, Filiaci VL, Mannel RS, Cohn DE, Matsumoto T, Tewari KS, et al. Carboplatin and paclitaxel for advanced endometrial cancer: Final overall survival and adverse event analysis of a phase III trial (NRG Oncology/GOG0209). J Clin Oncol 2020;38:3841-50.
12. Hashiguchi Y, Kasai M, Fukuda T, Ichimura T, Yasui T, Sumi T. Chemotherapy-induced neutropenia and febrile neutropenia in patients with gynecologic malignancy. Anticancer Drugs 2015;26:1054-60.
13. Laskey RA, Poniewierski MS, Lopez MA, Hanna RK, Secord AA, Gehrig PA, et al. Predictors of severe and febrile neutropenia during primary chemotherapy for ovarian cancer. Gynecol Oncol 2012;125:625-30.
14. Pimsi P, Therasakvichya S, Saengsukkasemsak N, Laocharoenkeat A. The incidence and risk factors of

severe neutropenia and febrile neutropenia due to chemotherapy among gynecologic cancer patients in Thailand. Eur J Gynaecol Oncol 2018;39:242-6.
15. Crawford J, Becker PS, Armitage JO, Blayney DW, Chavez J, Curtin P, et al. Myeloid growth factors, version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2017;15:1520-41.
16. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumors. Eur J Cancer 2011;47:8-32.