J Gynecol Oncol. 2020 Sep;31(5):e62
https://doi.org/10.3802/jgo.2020.31.e62
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Incidence and clinical course of septic shock in neutropenic patients during chemotherapy for gynecological cancers

Jigeun Yoo, Yuyeon Jung, Jung Hwan Ahn, Youn Jin Choi, Keun Ho Lee, Sooyoung Hur

Department of Obstetrics and Gynecology, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

Received: Dec 11, 2019
Revised: Apr 1, 2020
Accepted: Apr 10, 2020

Correspondence to
Sooyoung Hur
Department of Obstetrics and Gynecology, Seoul St. Mary's Hospital, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea.
E-mail: hursy@catholic.ac.kr

ORCID iDs
Jigeun Yoo
https://orcid.org/0000-0001-5359-8729
Yuyeon Jung
https://orcid.org/0000-0001-8862-3971
Jung Hwan Ahn
https://orcid.org/0000-0002-3372-1440
Youn Jin Choi
https://orcid.org/0000-0003-4699-2116
Keun Ho Lee
https://orcid.org/0000-0001-9005-7796
Sooyoung Hur
https://orcid.org/0000-0001-6563-2293

ABSTRACT

Objective: To identify the incidence and clinical course of septic shock combined with neutropenia during chemotherapy in gynecological cancer patients.
Methods: We retrospectively reviewed the medical records of all gynecological cancer patients who received intravenous chemotherapy between March 2009 and March 2018. Patients diagnosed with neutropenic septic shock (NSS) during the course of chemotherapy were identified. We calculated the overall incidence and mortality rate of NSS, and analyzed risk factors and clinical course.
Results: A total of 1,009 patients received 10,239 cycles of chemotherapy during the study period. Among these, 30 (3.0%) patients had 32 NSS events, of which 12 (1.2%) died. With respect to patient age during the first course of chemotherapy, the incidence of NSS after the age of 50 was significantly higher than that in patients under 50 (3.9% vs. 1.4%, p=0.034). As the number of chemotherapy courses increased, the incidence of NSS increased, and linear-by-linear association analysis showed a positive correlation (p=0.004). NSS events occurred on average 7.8 days after the last cycle of chemotherapy, and the median duration of vasopressor administration was 23.3 hours. The median age (64.0 vs. 56.5, p=0.017) and peak heart rate (149.5 min^{-1} vs. 123.5 min^{-1}, p=0.015) were significantly higher in the group of patients who subsequently died of NSS than in those who survived.
Conclusion: The overall incidence of NSS in gynecological cancer patients receiving chemotherapy was 3.0%, which is higher than previously estimated. Peak heart rate during NSS events may be an indicator for predicting survival.

Keywords: Adjuvant Chemotherapy; Chemotherapy-Induced Febrile Neutropenia; Gynecologic Neoplasms; Septic Shock

INTRODUCTION

In Korea, a total of 8,288 patients were diagnosed with cervical, ovarian, or endometrial cancer in 2015, and the absolute overall incidence of these major gynecologic cancers is increasing year by year [1]. Chemotherapy is used as a standard treatment for various gynecological malignancies [2-4], and has led to increased survival and reduced recurrence

Presentation
The 13rd workshop for young doctors, Korean Society of Gynecologic Oncology, oral presentation (Aug 17, 2019).

The 105th annual congress of Korean Society of Obstetrics and Gynecology, oral presentation (Sep 20-21, 2019).

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: Y.J., J.Y., A.J.H., C.Y.J., L.K.H., H.S.; Data curation: Y.J., A.J.H.; Formal analysis: Y.J., J.Y., A.J.H.; Investigation: Y.J., A.J.H.; Methodology: Y.J., C.Y.J., L.K.H., H.S.; Software: L.K.H.; Supervision: H.S.; Validation: Y.J., C.Y.J.; Visualization: C.Y.J.; Writing - original draft: Y.J., J.Y., A.J.H.; Writing - review & editing: H.S.

in gynecological cancer patients. Conversely, chemotherapy often causes myelosuppression, resulting in an increased risk of neutropenia and infection, which are the main associated complications [5-8]. These complications can also occur in patients with a longer life expectancy, such as those with complete remission status, and can directly lead to death [9]. Moreover, these complications can affect long-term survival by causing dose reduction and treatment delays [10,11]. The mortality rate of febrile neutropenia in solid tumors is reported to be approximately 8% [8,10], and septic shock, which is the most serious complication, has a mortality rate as high as 40% [12,13].

Roughly 10% of all cancer patients die from sepsis. The risk of sepsis is higher in patients with hematologic malignancies and relatively lower in those with gynecological cancers [14]. It is estimated that less than 1% of gynecological cancer patients who receive chemotherapy die from septic shock [2,14-16]; however, the exact figures are unknown, since very few studies have focused on septic shock in gynecological cancers, especially during the treatment of relapse cases. This renders it difficult for clinicians to select the optimal individualized patient treatment and to successfully prevent or treat chemotherapy-related septic shock.

The present study was conducted with a view to identifying the incidence and clinical course of septic shock combined with neutropenia during chemotherapy in gynecological cancer patients.

MATERIALS AND METHODS

The present study was approved by the Institutional Review Board (KC19RESI0512). We retrospectively reviewed the medical records of all gynecological cancer patients over 18 years of age who received intravenous chemotherapy between March 2009 and March 2018 at Seoul St. Mary's Hospital. Concurrent chemoradiotherapy and intraperitoneal chemotherapy were not included in this study. Patients diagnosed with septic shock combined with neutropenia during the course of chemotherapy or within 4 weeks of the last cycle were identified. Neutropenia was defined as a decrease in the absolute neutrophil count <500/μL or <1,000/μL and a predicted decline to <500/μL over the subsequent 48 hours [17,18]. Sepsis is defined as a dysregulated host response to infection and the presence of organ dysfunction, as presented by an increase in the Sequential Organ Failure Assessment score of 2 points or more [12]. Septic shock was defined as the presence of sepsis and hypotension that required vasopressors despite adequate volume resuscitation [12,19]. Events of septic shock with other accompanying causes of hypotension, such as hepatic failure, aspiration pneumonia, and gastrointestinal or intra-abdominal bleeding, were excluded. Moreover, patients who received vasopressors without proper initial fluid resuscitation were also excluded [20].

We defined neutropenic septic shock (NSS) as a combination of the aforementioned neutropenia and septic shock. All patients diagnosed with NSS were admitted to the intensive care unit and treated with initial fluid resuscitation, vasopressors, empirical broad-spectrum antibiotics, and granulocyte colony-stimulating factors, according to clinical practice guidelines [18,20,21].

We obtained patient characteristics including age, body mass index (BMI), medical comorbidities, primary cancer site, and International Federation of Gynecology and Obstetrics (FIGO) stage from the medical records. We also retrieved treatment data for each patient, including chemotherapy regimens, the number of courses and cycles of

chemotherapy, and the occurrence and timing of NSS. The course of chemotherapy is defined as a treatment plan consisting of several consecutive chemotherapy cycles, until the treatment is completed, stopped, or changed due to the progression of disease. Patients diagnosed with NSS were further examined for vital signs, laboratory findings, underlying diseases, past history of neutropenic fever, relapse and metastasis status, and duration of vasopressor administration. The primary outcome was the overall incidence and mortality rate of NSS. The secondary outcome was to identify the clinical course of NSS.

1. Statistical analysis

We conducted Fisher's exact test and the χ^2 test to determine the difference in NSS incidence according to clinical characteristics in gynecological cancer patients who received chemotherapy. The Student's t-test and Mann-Whitney test were performed to evaluate the clinical characteristics of NSS survivors and non-survivors. Univariate and multivariate logistic regression analyses were performed to determine the risk factors of NSS occurrence and survival. Receiver operating characteristics (ROC) curve analysis was performed to determine the optimal cut-off values for factors associated with death from NSS. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 1,009 patients received 10,239 cycles of chemotherapy during the study period. Among these, 30 (3.0%) patients had 32 NSS events, of which 12 (1.2%) died. The mortality rate of NSS was 37.5%. Two patients each had 2 NSS events during different chemotherapy regimens. Five patients died of unknown causes outside of the hospital during their chemotherapy course. A summary of the patients included in the present study can be found in **Table 1**.

Table 1. Summary of the study group

Variables	Without NSS (n=979)	With NSS (n=30)	p-value
Age at the first chemotherapy (yr)	53.0 (18.0–87.0)	57.0 (29.0–78.0)	**0.045**
<50	356 (36.4)	5 (16.7)	**0.032**
50–59	340 (34.7)	15 (50.0)	0.119
60–69	203 (20.7)	5 (16.7)	0.819
≥70	80 (8.2)	5 (16.7)	0.100
Body mass index (kg/m²)	22.3 (13.6–38.4)	23.3 (17.3–30.1)	0.346
Medical comorbidities			
Hypertension	121 (12.4)	3 (10.0)	>0.999
Diabetes	106 (10.8)	3 (10.0)	>0.999
Cancer site			0.547
Ovary	549 (56.1)	16 (53.3)	
Cervix	193 (19.7)	6 (20.0)	
Endometrium	118 (12.1)	6 (20.0)	
Primary peritoneal	64 (6.5)	1 (3.3)	
Uterine corpus	35 (3.6)	1 (3.3)	
Other	20 (2.0)	0	
FIGO cancer stage at diagnosis			0.128
I–II	367 (37.5)	7 (23.3)	
III–IV	612 (62.5)	23 (76.7)	
Total No. of chemotherapy received			**0.001**
One course	553 (55.6)	8 (26.7)	
Two or more courses	426 (44.4)	22 (73.3)	

All values are expressed as the median (range) or number (%).
Numbers marked in bold indicate p-values less than 0.05, which is considered statistically significant.
FIGO, International Federation of Gynecology and Obstetrics; NSS, neutropenic septic shock.

https://doi.org/10.3802/jgo.2020.31.e62

Table 2. Incidence of NSS according to chemotherapy regimen

Regimen	Patients	Courses	Cycles	Events of NSS
Carboplatin/paclitaxel	626	716	4,072	9 (1.44)
Carboplatin/docetaxel	171	196	1,102	5 (2.92)
Adriamycin/cisplatin	88	90	410	4 (4.55)
Single topotecan	79	83	413	2 (2.53)
Cisplatin/paclitaxel	71	77	419	1 (1.41)
Cisplatin/topotecan	69	69	235	2 (2.90)
Cisplatin/docetaxel	52	63	342	3 (5.77)
Single belotecan	45	45	249	1 (2.22)
Single vinorelbine weekly	35	35	140	1 (2.86)
Cisplatin/ifosfamide	28	31	129	1 (3.57)
Bevacizumab/paclitaxel/cisplatin	16	17	106	1 (6.25)
Bevacizumab/paclitaxel/carboplatin	8	8	50	1 (12.50)
Topotecan/ifosfamide	5	6	26	1 (20.00)

Values are expressed as number (%). Each percentage represents the number of NSS events among the total number of patients.
NSS, neutropenic septic shock.

The most common chemotherapy regimen was carboplatin (area under the curve [AUC] 5) plus paclitaxel (175 mg/m^2), which was administered to 626 patients. Nine (1.44%) of these patients developed NSS. The incidence of NSS for various chemotherapy regimens is summarized in **Table 2** and **Supplementary Table 1**.

1. Univariate and multivariate analysis

Table 3 presents the results of the univariate and multivariate analyses. With respect to patient age at the initiation of the first course of chemotherapy, the incidence of NSS after the age of 50 was significantly higher than that in patients under 50 (3.9% vs. 1.4%, p=0.034). This difference was also statistically significant in the multivariate analysis (p=0.031). A total of 561 patients received only one course of chemotherapy, 8 of which developed NSS. Patients who had 2 or more courses of chemotherapy showed a significantly higher incidence of NSS as compared with those who received only one course (4.9% vs. 1.4%, p=0.002). Regarding the cancer site, the incidence of NSS was 2.8% in patients with ovarian cancer, 3.0% in

Table 3. Univariate and multivariate logistic regression of associated factors

Factors	NSS/total	%	Univariate		Multivariate	
			RR (95% CI)	p-value	RR (95% CI)	p-value
Age at the first chemotherapy (yr)						
<50	5/361	1.4	Reference		Reference	
≥50	25/648	3.9	2.86 (1.08–7.53)	**0.034**	2.96 (1.12–7.82)	**0.029**
Medical comorbidities						
Hypertension	3/124	2.4	0.79 (0.24–2.64)	0.699	-	-
Diabetes	3/109	2.8	0.92 (0.28–3.07)	0.886	-	-
Cancer site						
Ovary cancer	16/565	2.8	Reference			
Cervical cancer	6/199	3.0	1.07 (0.41–2.77)	0.894	-	-
Endometrial cancer	6/124	4.8	1.75 (0.67–4.55)	0.255	-	-
Other	2/121	1.7	0.57 (0.13–2.54)	0.549	-	-
FIGO Cancer stage at diagnosis						
I–II	7/374	1.9	Reference			
III–IV	23/635	3.6	1.97 (0.84–4.64)	0.120	-	-
Total No. of chemotherapy received						
One course	8/564	1.4	Reference		Reference	
Two or more courses	22/445	4.9	3.57 (1.57–8.10)	**0.002**	3.65 (1.61–8.30)	**0.002**

Numbers marked in bold indicate p-values less than 0.05, which is considered statistically significant.
CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; NSS, neutropenic septic shock; RR, relative risk.

https://doi.org/10.3802/jgo.2020.31.e62

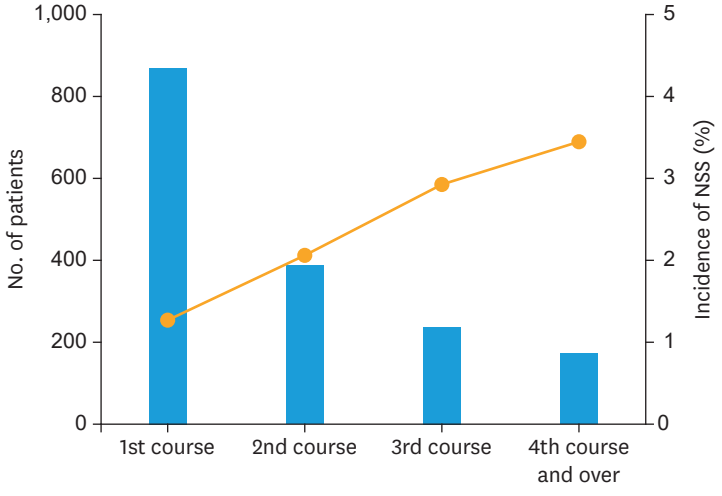
those with cervical cancer, and 4.8% in those with endometrial cancer, with no statistically significant differences. Concerning FIGO stage, patients with stages III–IV at initial diagnosis showed a higher incidence of NSS as compared with those with stages I–II; however, this difference was not statistically significant (3.6% vs. 1.9%, p=0.128).

2. Incidence of NSS according to the number of chemotherapy courses

Fig. 1 summarizes the incidence of NSS according to the number of chemotherapy courses. During the first course of chemotherapy, patients received an average of 5.5 cycles, with an NSS incidence of 1.3% (11/872) and an NSS-related mortality rate of 0.7%. During the second or higher courses of chemotherapy, patients received an average of 12.1 cycles, with an NSS incidence of 4.5% and an NSS-related mortality rate of 1.3%. As the number of chemotherapy courses increased, the incidence of NSS increased, and linear-by-linear association analysis showed a positive correlation (p=0.004). A total of 8.7% of patients received only 2 or fewer cycles during their first course of chemotherapy due to refusal of further treatment or transfer to another hospital. Even excluding these patients, a positive correlation between the number of chemotherapy courses and the incidence of NSS was maintained (p=0.035).

3. Clinical course of NSS events

Table 4 demonstrates a comparison of the clinical characteristics of NSS events based on survival. NSS events occurred on average 7.8 days after the last cycle of chemotherapy, with all events occurring within 14 days. In the univariate analysis, median age (64.0 vs. 56.5, p=0.017), initial heart rate (122.5 min^{-1} vs. 112.0 min^{-1}, p=0.039), and peak heart rate during the events (149.5 min^{-1} vs. 123.5 min^{-1}, p=0.002) were significantly higher in the group of patients who subsequently died. In the multivariate analysis, age (p=0.017) and peak heart rate (p=0.015) were identified as risk factors for death from NSS. ROC curve analysis was performed for the peak heart rate (**Supplementary Fig. 1**). The AUC was 0.82 (95% confidence interval=0.66–0.97; sensitivity and specificity 83.3% and 75.0%, respectively; p=0.003) and the optimal cut-off value was 141.0 min^{-1}. The median duration of vasopressor



	1st course	2nd course	3rd course	4th course and over
No. of patients	872	390	240	174
Patients with NSS	11	8	7	6
Incidence of NSS	1.26%	2.05%	2.92%	3.45%

Fig. 1. Incidence of NSS for each chemotherapy course. A positive correlation was found between the number of chemotherapy courses and the incidence of NSS (linear-by-linear association analysis, p=0.004).
NSS, neutropenic septic shock.

https://doi.org/10.3802/jgo.2020.31.e62

Table 4. Univariate and multivariate analysis of factors for survival during NSS events (n=32)

Factors	Events of survive (n=20)	Events of death (n=12)	p-value	
			Univariate	Multivariate
Age (yr)	56.5 (29–66)	64.0 (46–78)	**0.012**	**0.020**
Mean body mass index (kg/m^2)	24.1 (14.7–28.4)	23.0 (17.1–27.5)	0.829	-
ECOG performance status			0.150	-
I–II	14 (70.0)	5 (41.7)		
III–IV	6 (30.0)	7 (58.3)		
Type of cancer				
Ovarian	12 (60.0)	5 (41.7)	0.437	-
Cervical	3 (15.0)	3 (25.0)	-	-
Endometrial	3 (15.0)	4 (33.3)	-	-
Other	2 (10.0)	0	-	-
FIGO stage				
I–II	3 (15.0)	4 (33.3)	0.379	-
III–IV	17 (85.0)	8 (66.7)	-	-
Recurrence status				
Primary treatment	3 (15.0)	5 (41.7)	0.116	-
Recurrent disease	17 (85.0)	7 (58.3)	-	-
Past history of neutropenic fever	8 (40.0)	4 (33.3)	>0.999	-
Comorbidities				
Hypertension	2 (10.0)	2 (16.7)	0.620	-
Diabetes	3 (15.0)	1 (8.3)	>0.999	-
Lung metastasis	2 (10.0)	4 (33.3)	0.165	-
Splenectomy	5 (25.0)	2 (16.7)	0.683	-
Ileostomy	2 (10.0)	3 (25.0)	0.338	-
Carcinomatosis peritonei	7 (35.0)	5 (41.7)	0.724	-
Deep vein thrombosis	7 (35.0)	1 (8.3)	0.204	-
Factors at the initial diagnosis of NSS				
Time from cancer diagnosis (mo)	20.5 (1.0–85.0)	19.0 (0–95.0)	0.687	-
Time from the last chemotherapy (day)	8.0 (3.0–14.0)	7.0 (4.0–14.0)	0.890	-
No. of courses of chemotherapy received	2.5 (1.0–8.0)	1.5 (1.0–6.0)	0.209	-
Heart rate (/min)	112.0 (84.0–140.0)	122.5 (101.0–184.0)	**0.039**	0.460
Hemoglobin (mg/dL)	10.3 (7.0–13.3)	9.6 (5.6–13.8)	0.720	-
Factors during NSS treatment				
Peak body temperature (°C)	39.2 (37.3–40.4)	38.1 (35.6–40.4)	0.067	-
Peak heart rate (/min)	123.5 (110.0–180.0)	149.5 (120.0–200.0)	**0.002**	**0.015**
The lowest neutrophil count (mg/dL)	20.0 (0–500.0)	35.0 (0–260.0)	>0.999	-
The highest creatinine concentration (mg/dL)	1.2 (0.64–4.1)	2.0 (1.3–4.3)	0.146	-
The highest CRP concentration (mg/dL)	30.2 (10.0–35.7)	28.2 (13.8–34.1)	0.687	-
Duration of the vasopressor administration (hr)*	38.0 (6.0–140.8)	20.9 (0.2–50.2)	**0.036**	-

All values are expressed as the median (range) or number (%).
Numbers marked in bold indicate p-values less than 0.05, which is considered statistically significant.
CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; NSS, neutropenic septic shock.
*Multivariate analysis was not performed, since this difference is thought to be the consequence of events in the group of patients who died and had no recovery period from septic shock.

administration was 23.3 hours in total, 38.0 hours in the group of patients who survived and 20.9 hours in the group of patients who subsequently died (p=0.036). The peak body temperature, hemoglobin level at NSS diagnosis, lowest neutrophil count, and highest C-reactive protein and creatinine levels did not differ between the 2 groups. One patient who subsequently died had hypothermia, and one who subsequently died and 2 who survived had normothermia. Pathogens were identified in 56.3% of blood cultures and 37.5% of urine cultures. The identified pathogens are summarized in **Table 5**.

https://doi.org/10.3802/jgo.2020.31.e62

Table 5. Identified pathogens in blood and urine cultures

Factors	Events of survive (n=20)	Events of death (n=12)
Patients with isolated pathogen	15 (75.0)	10 (83.3)
Blood culture		
Escherichia coli, ESBL (−)	3 (15.0)	3 (25.0)
Escherichia coli, ESBL (+)	2 (10.0)	0
Klebsiella pneumoniae	2 (10.0)	2 (16.7)
Enterobacter cloacae	2 (10.0)	0
Enterobacter cancerogenus	1 (5.0)	0
Pseudomonas aeruginosa	0	1 (8.3)
Enterococcus	0	1 (8.3)
Bacillus	1 (5.0)	0
Not identified	9 (45.0)	5 (41.7)
Urine culture		
Escherichia coli, ESBL (+)	2 (10.0)	0
Enterococcus	3 (15.0)	2 (16.7)
Corynebacterium	1 (5.0)	0
Staphylococcus aureus	0	1 (8.3)
Yeast	0	1 (8.3)
Mixed	2 (10.0)	0
Not identified	12 (60.0)	8 (66.7)

ESBL, extended-spectrum β-lactamase.

DISCUSSION

This was a retrospective study to investigate the incidence and clinical features of NSS induced by chemotherapy in gynecological cancer patients. Although neutropenic sepsis and septic shock are the most fatal chemotherapy-related complications, research in the field of gynecological malignancies is lacking. Moreover, despite the fact that many patients with recurrent gynecological malignancies receive chemotherapy, few studies have been conducted in the recurrence setting. Therefore, the incidence of NSS can only be estimated from clinical trial toxicity data. However, this approach differs from real-world studies, since most clinical trials do not provide sufficient toxicity data for sepsis, and target highly selected patients with a good performance status [9,10]. Moreover, clinical trials monitor the toxicity over short time-periods and are therefore inadequate for determining the overall incidence of NSS in patients who are treated repeatedly over several years.

Markman et al. [2] reported one (0.3%) neutropenic-related death in a retrospective study of 323 primary and recurrent gynecological cancer patients. Sharma et al. [15] reported no NSS-related deaths in a study of 125 patients with ovarian cancer who received first-line chemotherapy. Several large clinical trials conducted for primary or recurrent gynecologic malignancies have reported a septic shock-related mortality rate of 0%–0.9% [16,22-27]. This allows us to estimate that the incidence of septic shock is 0%–2.25%, since mortality from septic shock is known to be roughly 40% [12]. Our overall NSS incidence (3.0%) is higher than that reported in previous studies, especially in patients who received second or higher courses of chemotherapy (4.9%). The patient group and observation period in our study differ from those in previous studies, since we analyzed the total chemotherapy period of the patients to better reflect the exact overall incidence of NSS. The patients analyzed in the present study received an average of 2.2 courses and 10.1 cycles of chemotherapy. In addition, 23.8% were heavily treated patients who received 3 or more courses of chemotherapy; however, since 99.2% of the patients included in our study were Korean, ethnic differences in hematological toxicity may have affected the results. Ethnic diversity in drug response and toxicity results from the combined interaction of many factors, such as differences

in genetics, the environment, drug–drug interactions, and local practice. Several studies have shown that greater toxicity and responses to chemotherapy are observed in Asians as compared with Caucasians [28]. Takei et al. [29] conducted a feasibility study of carboplatin and paclitaxel in Japanese ovarian cancer patients, reporting that grade 4 neutropenia was observed in 80% of patients. Kim et al. [30] showed that the incidence of febrile neutropenia during doxorubicin/cyclophosphamide and docetaxel chemotherapy in Korean breast cancer patients was 29.5%, which is higher than that reported in previous studies conducted in Western countries.

The increase in NSS incidence with increasing numbers of chemotherapy courses identified in our study appears to be the consequence of increased exposure to chemotherapy and cumulative myelosuppression by carboplatin [31,32]. It is also thought to be the result of deterioration of performance status due to repeated treatment, in addition to cancer progression. Old age, poor performance status, low BMI, advanced disease, prior chemotherapy, and the presence of major comorbidities are known risk factors for the development of neutropenic fever [33,34].

Previous studies have reported differences in the incidence of neutropenia and neutropenic fever according to chemotherapy regimen. In a pooled analysis of the adverse effects of several randomized trials, Covens et al. [35] found that carboplatin produced grade 3 or 4 hematological adverse effects more frequently than cisplatin. Further, docetaxel, administered as a single agent or in combination, has been shown to cause a higher incidence and severity of neutropenia than paclitaxel [2,36]. The incidence of NSS is also expected to vary according to chemotherapy regimen, but this was not statistically verified in the present study. Each chemotherapy regimen was administered in a different clinical situation, such as varied cancer sites, stage, recurrence status, and platinum sensitivity, and NSS events may have been affected by the chemotherapeutic agents administered in previous courses. Considering these points, the number of NSS events that occurred during each regimen was too small to verify statistically. Whether chemotherapy regimens with a higher risk of neutropenia also increase the incidence of NSS is a question that needs to be verified by further large-scale studies.

In the initial treatment of septic shock, adequate volume resuscitation often results in a decrease in heart rate; however, expression of sympathetic overstimulation due to activation of peripheral afferent fibers by ischemia and inflammation causes persistent tachycardia [37]. Previous analysis of 48 patients with septic shock found that an initial heart rate of <106 min^{-1} and <95 min^{-1} significantly predicts survival [38]. Through analysis of NSS events in the present study, it was found that peak heart rate during NSS events was related to death, which was confirmed by ROC curve analysis, with a cut-off value of 141 min^{-1}. However, predefining a threshold value for heart rate is difficult, since it must be individualized in the context of the patient's overall hemodynamic condition, pre-existing comorbidities, and drug effects [37]; therefore, the cut-off value reported in the present study must be verified in further studies.

The definition and treatment of sepsis in neutropenic cancer patients follow the general treatment guidelines for sepsis [17]. In 2014, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine redefined septic shock, adding a serum lactate level of 2 mmol/L or higher to the diagnostic criteria [12]. In the present study, we did not report the lactate level, since patients with fluid-resistant hypotension but a lactate level of 2 mmol/L or less also have a high mortality rate of over 30% [12]. Initial resuscitation in

this subset of patients is similar to that in those with a lactate level greater than 2 mmol/L [20]. Moreover, we could not identify baseline lactate levels in 55.3% of septic shock events. Our hospital routinely measures the lactate levels in septic shock patients using blood gas analyzers installed in the intensive care unit and emergency department, and we can check the results on the screen or print them out. However, since certain values, including lactate levels, were not transferred to the electronic chart prior to 2017, lactate levels could not be identified in several NSS events.

To the best of our knowledge, this is the largest study to analyze the incidence and clinical course of NSS in patients receiving chemotherapy in the field of gynecological cancer. There exist several limitations to the present study, however, which are as follows: Firstly, all the disadvantages that arise as a result of retrospective analysis are present. Secondly, due to the rarity of NSS, the total number of NSS events observed in the present study is small. Thirdly, risk factors for NSS occurrence were not analyzed according to performance status, dose reduction, or prior pelvic radiation therapy.

In conclusion, for patients with gynecological cancer treated with chemotherapy, it was found that the overall incidence of NSS was 3.0%, and for patients who received second or higher courses of chemotherapy, it was 4.9%. An age greater than 50 years old at the time of the initial course and second or higher courses of chemotherapy was found to be a risk factor for developing NSS. Patients with these risk factors may be candidates for prophylactic use of granulocyte-colony stimulating factors, and further studies are needed. The mean age and peak heart rate during NSS events were significantly higher in patients who subsequently died from NSS than in those who survived.

ACKNOWLEDGMENTS

We would like to thank the Department of Biostatics, Clinical Research Coordinating Center, The Catholic University of Korea for statistical support, and Dr. S. J. Lee, Seoul St. Mary's Hospital, The Catholic University of Korea for his comments on this manuscript.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Incidence of NSS according to the chemotherapy regimen and the number of chemotherapy courses

Click here to view

Supplementary Fig. 1

The ROC curve of the peak heart rate during neutropenic septic shock events for predicting death. Optimal cut-off value=141.0 min^{-1}; AUC=0.82 (95% confidence interval=0.66–0.97; sensitivity and specificity 83.3% and 75.0%, respectively; p=0.003).

Click here to view

REFERENCES

1. Lim MC, Won YJ, Ko MJ, Kim M, Shim SH, Suh DH, et al. Incidence of cervical, endometrial, and ovarian cancer in Korea during 1999–2015. J Gynecol Oncol 2019;30:e38.
PUBMED | CROSSREF
2. 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.
PUBMED | CROSSREF
3. Reed NS, Sadozye AH. Update on chemotherapy in gynaecological cancers. Obstet Gynecol 2016;18:182-8.
CROSSREF
4. Chu CS, Rubin SC. Basic principles of chemotherapy. In: Di Saia PJ, Creasman WT, Mannel RS, McMeekin DS, Mutch DG, editors. Clinical gynecologic oncology. 9th ed. Philadelphia, PA: Elsevier; 2018. p. 449-69.
5. Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, et al. Management of febrile neutropaenia: ESMO clinical practice guidelines. Ann Oncol 2016;27:v111-8.
PUBMED | CROSSREF
6. Lyman GH, Michels SL, Reynolds MW, Barron R, Tomic KS, Yu J. Risk of mortality in patients with cancer who experience febrile neutropenia. Cancer 2010;116:5555-63.
PUBMED | CROSSREF
7. Okera M, Chan S, Dernede U, Larkin J, Popat S, Gilbert D, et al. A prospective study of chemotherapy-induced febrile neutropenia in the South West London Cancer Network. Interpretation of study results in light of NCAG/NCEPOD findings. Br J Cancer 2011;104:407-12.
PUBMED | CROSSREF
8. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2015;33:3199-212.
PUBMED | CROSSREF
9. Kuderer NM, Wolff AC. Enhancing therapeutic decision making when options abound: toxicities matter. J Clin Oncol 2014;32:1990-3.
PUBMED | CROSSREF
10. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106:2258-66.
PUBMED | CROSSREF
11. Gunderson CC, Farrell R, Dinh BC, Thomas ED, Vesely SK, Lauer JK, et al. Inpatient versus outpatient management of neutropenic fever in gynecologic oncology patients: is risk stratification useful? Gynecol Oncol 2013;130:411-5.
PUBMED | CROSSREF
12. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.
PUBMED | CROSSREF
13. Legrand M, Max A, Peigne V, Mariotte E, Canet E, Debrumetz A, et al. Survival in neutropenic patients with severe sepsis or septic shock. Crit Care Med 2012;40:43-9.
PUBMED | CROSSREF
14. Williams MD, Braun LA, Cooper LM, Johnston J, Weiss RV, Qualy RL, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. Crit Care 2004;8:R291-8.
PUBMED | CROSSREF
15. Sharma S, Rezai K, Driscoll D, Odunsi K, Lele S. Characterization of neutropenic fever in patients receiving first-line adjuvant chemotherapy for epithelial ovarian cancer. Gynecol Oncol 2006;103:181-5.
PUBMED | CROSSREF
16. Hoskins P, Vergote I, Cervantes A, Tu D, Stuart G, Zola P, et al. Advanced ovarian cancer: phase III randomized study of sequential cisplatin-topotecan and carboplatin-paclitaxel vs carboplatin-paclitaxel. J Natl Cancer Inst 2010;102:1547-56.
PUBMED | CROSSREF
17. Kochanek M, Schalk E, von Bergwelt-Baildon M, Beutel G, Buchheidt D, Hentrich M, et al. Management of sepsis in neutropenic cancer patients: 2018 guidelines from the Infectious Diseases Working Party (AGIHO) and Intensive Care Working Party (iCHOP) of the German Society of Hematology and Medical Oncology (DGHO). Ann Hematol 2019;98:1051-69.
PUBMED | CROSSREF

18. National Comprehensive Cancer Network (US). NCCN Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections (version 1. 2019). Fort Washington, PA: National Comprehensive Cancer Network; 2019 [cited 2019 Nov 26]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf.
19. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Intensive Care Med 2003;29:530-8.
PUBMED | CROSSREF
20. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304-77.
PUBMED | CROSSREF
21. Penack O, Becker C, Buchheidt D, Christopeit M, Kiehl M, von Lilienfeld-Toal M, et al. Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO). Ann Hematol 2014;93:1083-95.
PUBMED | CROSSREF
22. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, Gebski V, Heywood M, Vasey PA, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol 2010;28:3323-9.
PUBMED | CROSSREF
23. Pignata S, Scambia G, Ferrandina G, Savarese A, Sorio R, Breda E, et al. Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. J Clin Oncol 2011;29:3628-35.
PUBMED | CROSSREF
24. Kitagawa R, Katsumata N, Shibata T, Kamura T, Kasamatsu T, Nakanishi T, et al. Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase iii trial JCOG0505. J Clin Oncol 2015;33:2129-35.
PUBMED | CROSSREF
25. Aghajanian C, Filiaci V, Dizon DS, Carlson JW, Powell MA, Secord AA, et al. A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. Gynecol Oncol 2018;150:274-81.
PUBMED | CROSSREF
26. Matei D, Filiaci V, Randall ME, Mutch D, Steinhoff MM, DiSilvestro PA, et al. Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer. N Engl J Med 2019;380:2317-26.
PUBMED | CROSSREF
27. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 2012;30:2039-45.
PUBMED | CROSSREF
28. O'Donnell PH, Dolan ME. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. Clin Cancer Res 2009;15:4806-14.
PUBMED | CROSSREF
29. Takei Y, Suzuki M, Ohwada M, Saga Y, Kohno T, Machida S, et al. A feasibility study of paclitaxel and carboplatin therapy in Japanese patients with epithelial ovarian cancer. Oncol Rep 2003;10:951-5.
PUBMED | CROSSREF
30. Kim CG, Sohn J, Chon H, Kim JH, Heo SJ, Cho H, et al. Incidence of febrile neutropenia in Korean female breast cancer patients receiving preoperative or postoperative doxorubicin/cyclophosphamide followed by docetaxel chemotherapy. J Breast Cancer 2016;19:76-82.
PUBMED | CROSSREF
31. Dunton CJ. Management of treatment-related toxicity in advanced ovarian cancer. Oncologist 2002;7 Suppl 5:11-9.
PUBMED | CROSSREF
32. Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN, et al. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol 1992;10:520-8.
PUBMED | CROSSREF
33. 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.
PUBMED | CROSSREF

34. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: a systematic review. Crit Rev Oncol Hematol 2014;90:190-9.
PUBMED | CROSSREF
35. Covens A, Carey M, Bryson P, Verma S, Fung Kee Fung M, Johnston M. Systematic review of first-line chemotherapy for newly diagnosed postoperative patients with stage II, III, or IV epithelial ovarian cancer. Gynecol Oncol 2002;85:71-80.
PUBMED | CROSSREF
36. Markman M. Management of toxicities associated with the administration of taxanes. Expert Opin Drug Saf 2003;2:141-6.
PUBMED | CROSSREF
37. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA 2013;310:1683-91.
PUBMED | CROSSREF
38. Parker MM, Shelhamer JH, Natanson C, Alling DW, Parrillo JE. Serial cardiovascular variables in survivors and nonsurvivors of human septic shock: heart rate as an early predictor of prognosis. Crit Care Med 1987;15:923-9.
PUBMED | CROSSREF