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

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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.
Neutropenic septic shock in gynecological cancer

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 $\chi^2$ 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.

| 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)        |         |
| 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/m$^2$)                  | 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                                |                    |                 |         |
| 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.
The most common chemotherapy regimen was carboplatin (area under the curve [AUC] 5) plus paclitaxel (175 mg/m²), 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.

### 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 (2.33%)     |
| 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.

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#### 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...
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...
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/m²) | 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) | 0.437 | - | |
| III–IV | 6 (30.0) | 7 (58.3) | - | - | |
| Type of cancer |                      |                        |         |            |              |
| Ovarian | 12 (60.0) | 5 (41.7) |          |          |              |
| 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 (10–85.0) | 19.0 (9–95.0) | 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.

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.
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

| 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.
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.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
In incidence of NSS according to the chemotherapy regimen and the number of chemotherapy courses

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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).

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