# Evaluation of primary prophylaxis with granulocyte colony-stimulating factor for epithelial ovarian cancer

**K. Matsui, T. Mori, M. Sawada, H. Kuroboshi, H. Tatsumi, T. Yoshioka, M. Akiyama T. Yamamoto, K. Iwasaku, J. Kitawaki**

*Department of Obstetrics and Gynecology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto (Japan)*

**Summary**

*Purpose:* Primary prophylaxis with G-CSF has been used to minimize myelosuppression caused by anticancer agents and to avoid severe neutropenia. The authors retrospectively examined the value of primary prophylaxis using granulocyte colony-stimulating factor (G-CSF) for epithelial ovarian cancer. *Materials and Methods:* From 2001 to 2010, 105 patients with ovarian cancer receiving chemotherapy in the present hospital were divided into two groups: one received primary prophylaxis with G-CSF and the other did not receive it in compliance with the guidelines for G-CSF usage. The incidence of febrile neutropenia (FN), degree of neutropenia, frequency of G-CSF administration, number of days of hospitalization, progression-free survival (PFS), and overall survival (OS) were evaluated. *Results:* Neutrophils decreased almost equally and the length of hospitalization was not significantly lower between the groups. Five-year PFS or OS showed no significant difference either. *Conclusions:* Primary prophylaxis with G-CSF in chemotherapy for epithelial ovarian cancer could be of low significance.

*Key words:* Epithelial ovarian cancer; Primary prophylaxis; Granulocyte colony-stimulating factor; Febrile neutropenia.

## Introduction

Neutropenia is one aspect of bone marrow toxicity caused by many anticancer agents. In neutropenia patients with fever, a serious bacterial infection is a likely complication and requires close management. The frequency of serious infection in patients with neutrophil counts of 1,000 neutrophils/mm$^3$ or more is around 5%, while those in patients with neutrophil counts of < 500 and < 100 neutrophils/mm$^3$ are 19% and 28%, respectively; the frequency increases in proportion to the severity of neutropenia [1]. Granulocyte colony-stimulating factor (G-CSF) is used as a strong weapon against serious infection associated with neutropenia. Conventionally, primary prophylaxis with G-CSF has been used to minimize myelosuppression caused by anticancer agents and to avoid severe neutropenia. However, in clinical situations, G-CSF is often used even if patients experience only mild neutropenia, and in some cases that require frequent visits to the clinic or hospital for reasons such as examinations of blood samples. More recently, G-CSF is not generally recommended in various guidelines unless chemotherapy associated with frequent febrile neutropenia (FN) is administered [2, 3]. Regarding the validity of G-CSF administration in patients with epithelial ovarian cancer from the perspective of quality of life (QOL) and medical economics, there has so far been no detailed report indicating whether G-CSF can reduce the dosage of antibacterial agents and improve patient prognosis.

In this study, the authors retrospectively examined the value of primary prophylaxis using G-CSF for epithelial ovarian cancer, by comparing two groups in which primary prophylaxis with G-CSF was either used, or not used, in patients with ovarian cancer who received chemotherapy.

## Materials and Methods

From 2001 to 2010, 105 patients with ovarian cancer (initial onset or recurrence) received chemotherapy (taxane and platinum-based combination therapy) in the present hospital. They were divided into two groups: one consisting of patients who received primary prophylaxis with G-CSF (primary prophylaxis group) and the other with patients who did not receive G-CSF in compliance with the guidelines for use of G-CSF issued by the Japan Society of Clinical Oncology (compliance group); these two groups were then compared. The items evaluated were the incidence of FN, degree of neutropenia, frequency of G-CSF administration, number of days of hospitalization, progression-free survival (PFS), and overall survival (OS).

FN was defined as a condition of < 500 neutrophils/mm$^3$, or a condition of < 1,000 neutrophils/mm$^3$ with the expectation of a drop to 500 neutrophils/mm$^3$ or less, together with body temperature of 38°C or higher or fever (37.5°C or more) that continued for at least one hour [4].

The degree of neutropenia was evaluated as the lowest number of neutrophils seen during the entire treatment period. For the frequency of G-CSF use, 75 μg of filgrastim and 50 μg of lenograstim/nartograstim were considered to offer equivalent efficacies, and therefore each was counted as one dose.

Statistical analysis was performed by the Student *t* test and Chi-square ($\chi^2$) test for the comparison between groups, and survival analysis was performed by the Kaplan-Meier method; a value of $p < 0.05$ was considered statistically significant.

Revised manuscript accepted for publication March 28, 2013

Table 1. — *Patient characteristics.*

| | | Primary prophylaxis group n=38 | Compliance group n=67 | P |
|---|---|---|---|---|
| Age (year) | Median | 57 | 59 | 0.88 |
| | Range | 38-77 | 26-74 | |
| ECOG performance | 0 | 31 | 58 | 0.49 |
| | 1 | 7 | 9 | 0.46 |
| | 2 | 0 | 0 | 0.99 |
| Stage of disease | I | 9 | 24 | 0.19 |
| | II | 2 | 2 | 0.55 |
| | III | 23 | 35 | 0.41 |
| | IV | 4 | 6 | 0.79 |
| Histological type | Serous | 25 | 35 | 0.18 |
| | Mucinous | 5 | 5 | 0.34 |
| | Clear cell | 5 | 18 | 0.10 |
| | Endometrioid | 3 | 7 | 0.67 |
| | Other | 0 | 2 | 0.28 |

The statistical difference was determined by Student's *t* and $\chi^2$ test.

Table 2. — *Incidence of FN between two groups.*

| | Primary prophylaxis group | Compliance group | Total |
|---|---|---|---|
| FN (+) | 6 (15.8%) | 6 (9.0%) | 12 |
| FN (-) | 32 (84.2%) | 61 (91.0%) | 93 |
| Total | 38 | 67 | 105 |

P = 0.29

The statistical difference was determined by $\chi^2$ te

Table 3. — *Cases with FN from two groups.*

Primary prophylaxis group

| Case | Age | Stage | PS | Initial onset or recurrence | Antibacterial agent used (/day) | Administration period (days) | Pathogenic bacteria detected | MASCC score |
|---|---|---|---|---|---|---|---|---|
| 1 | 57 | IIc | 1 | Recurrence | CFPM 2g | 5 | Undetected | 22 |
| 2 | 57 | IIIc | 0 | Recurrence | IPM/CS 1g | 4 | E.Coli (blood) | 20 |
| 3 | 57 | IIIc | 1 | Recurrence | CFPM 2g | 3 | Undetected | 22 |
| 4 | 41 | IV | 0 | Recurrence | FMOX 3g | 4 | Undetected | 22 |
| 5 | 68 | IV | 1 | Recurrence | CFPM 2g | 3 | Undetected | 20 |
| 6 | 60 | IIIc | 0 | Recurrence | CFPM 2g | 3 | E.Coli (vagina) | 22 |

Compliance group

| Case | Age | Stage | PS | Initial onset or recurrence | Antibiotics agent used (/day) | Administration period (days) | Pathogenic bacteria detected | MASCC score |
|---|---|---|---|---|---|---|---|---|
| 7 | 59 | IIIc | 1 | Initial onset | CZOP 1g | 10 | Undetected | 22 |
| 8 | 62 | IIIc | 0 | Recurrence | CFPM 2g | 3 | E.Coli (urine) | 20 |
| 9 | 39 | IIIc | 0 | Initial onset | IPM/CS 1g | 3 | Undetected | 22 |
| 10 | 56 | IIIc | 1 | Recurrence | MEPM 1g | 7 | Undetected | 22 |
| 11 | 70 | IIIc | 1 | Recurrence | CFPM 2g | 6 | Undetected | 20 |
| 12 | 53 | IIIc | 0 | Recurrence | MEPM 1g | 7 | Undetected | 22 |

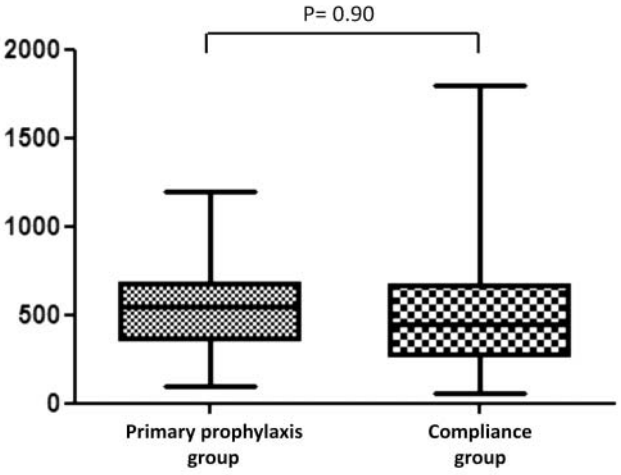


Figure 1. — Degree of neutropenia between two groups. There was no difference in the degree of neutropenia between two groups ($p = 0.90$). Statistical analysis was performed by Student t test and $p < 0.05$ was considered statistically significant.

## Results

Of 105 patients with epithelial ovarian cancer who received chemotherapy, 38 patients were assigned to the primary prophylaxis group, and 67 patients were assigned to the compliance group. Table 1 shows patient characteristics in each group. Age at the time of chemotherapy administration, performance status (PS), progression stage of ovarian cancer, and histological type were examined, but there were no significant differences between the groups.

The incidence of FN was 15.8% (six patients) in the primary prophylaxis group and 9% (six patients) in the compliance group; the primary prophylaxis group showed a tendency to include more cases of FN in comparison to the compliance group (Table 2). The degree of neutropenia was not different between the groups ($p = 0.90$; Figure 1): statistical analysis was performed by Student t test and $p < 0.05$ was considered statistically significant. Neutrophils decreased almost equally in patients who received and did not receive primary prophylaxis. In addition, the length of hospitalization was not significantly lower in either group ($p = 0.20$).

Figures 2 and 3 shows the results of prognosis analysis by the Kaplan-Meier method. Five-year PFS tended to be higher in the primary prophylaxis group than in the compliance group (41.4% vs 31.3%; log rank $p = 0.26$; Figure 2). Five-year OS showed no significant difference between the groups (36.8% vs 50.0%; log-rank $p = 0.64$; Figure 3).

Furthermore, a total of 12 patients with FN from both groups were examined (Table 3). The mean age of onset of FN was 56.6 years (range 39-70), with FN occurring in relatively younger patients. FN was frequently observed in patients with advanced ovarian cancer such as Stage III and IV, patients with poor PS, and patients with recurrent ovarian cancer.

All patients with FN who were treated with a fourth-generation cephem, such as cefepime dihydrochloride (CFPM) or carbapenem antibiotics (imipenem/cilastatin [IPM/CS] or meropenem [MEPM]), showed complete response.

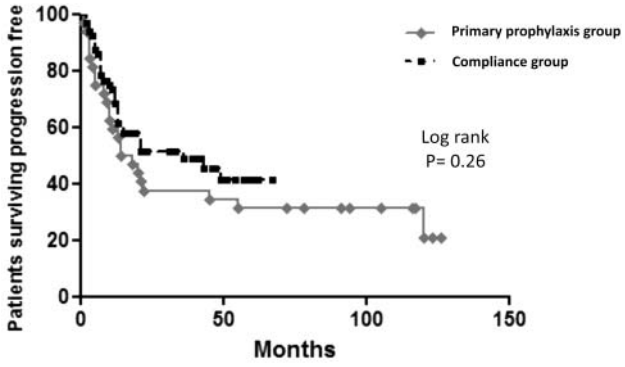


Figure 2. — Progression free survival (PFS). The prognosis was analyzed using the Kaplan-Meier method. PFS showed no significant difference between the groups (log rank $p = 0.26$).

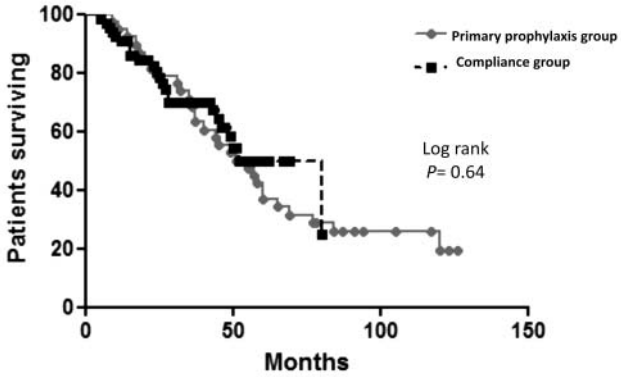


Figure 3. — Overall survival (OS) between two groups. The prognosis was analyzed using the Kaplan-Meier method. OS showed no significant difference between the groups (rank $p = 0.64$).

Pathogenic bacteria causing FN were detected very infrequently by blood cultures (8.3%), but the rate of detection was 23.1% when urine cultures and cultured vaginal discharge were included. All of the detectable pathogenic bacteria were *escherichia coli*.

## Discussion

In Japan, the number of deaths from ovarian cancer has been obviously increasing, and this form of cancer has the highest mortality among gynecological malignant tumors [5]. Although the first treatment is conducted by surgical procedure, chemotherapy is often performed for patients at risk of recurrence even in the initial stage. For patients with advanced cancer who cannot undergo debulking surgery as the primary operation, chemotherapy is the main treatment method. Furthermore, it is reported that about 55% of patients with ovarian cancer relapse within two years, and most of them require chemotherapy [6].

FN is one of the severe complications associated with neutropenia caused by chemotherapy, and requires particular care. The present study showed that in patients with initial or recurrent ovarian cancer who were treated with taxane- and platinum-based combination therapy, the incidence of FN was 9% in the group without G-CSF prophylaxis. However, Crawford *et al.* reported that the incidence of FN was 77% when patients did not receive G-CSF for small cell lung cancer [7]. In addition, Pettengell *et al.* reported that the incidence of FN was 85% when patients with non-Hodgkin's lymphoma did not receive G-CSF as a part of the CHOP treatment regimen [8], and they recommended primary prophylaxis with G-CSF. In comparison to these reports, the incidence of FN in patients treated for ovarian cancer was extremely low in the present study. Based on the American Society of Clinical Oncology (ASCO) guidelines proposed in 2006, which recommend primary prophylaxis with G-CSF when the risk of developing FN is over 20% [3], the present results suggest that primary prophylaxis with G-CSF is of low significance in the treatment of ovarian cancer.

A meta-analysis by Kuderder *et al.* reported that risk of FN, mortality of infection, and mortality during chemotherapy were decreased by 40% or more with primary prophylaxis with G-CSF for solid cancers and malignant lymphoma [9]. However, in the present study, no early deaths caused by chemotherapy-induced infection were seen in either group.

There are many reports that G-CSF administration results in significant shortening of the length of neutropenia and hospitalization, and in decreased mortality due to infection, but it does not extend survival time [10-12]. In this study, the prognosis of the primary prophylaxis group was not improved in comparison to that of the compliance group, as shown in Figure 2. Furthermore, significant shortening of the length of hospitalization was not observed. It can be concluded that primary prophylaxis with G-CSF is of low significance in the treatment of ovarian cancer.

On the other hand, the 2006 ASCO guidelines mention that primary prophylaxis with G-CSF is appropriate for patients with concurrent risk factors, even if the incidence of FN was 20% or less. Concurrent risk factors are defined as age greater than 65 years, poor PS, history of FN, high-level previous treatment (for example, extensive radiation exposure), hematopenia caused by the bone marrow infiltration, poor nutrition, open wound or active infection, chemotherapy with radiotherapy, and advanced cancer. In individual examinations of the 12 patients with ovarian cancer who developed FN in this study, FN was found relatively more frequently in patients with recurrent cancer, poor PS, or advanced cancer. FN was observed even in patients who were relatively young, suggesting that age is not an important risk factor in patients with ovarian cancer.

The Multinational Association of Care in Cancer

(MASCC) score is generally used to determine risk in patients with FN [12]. The symptoms of many patients in this study were mild, and as shown in Table 3, most of the patients showed low risk at evaluation using the MASCC score.

With respect to antibacterial agents, treatment with fourth-generation cephem antibiotics or carbapenem antibiotics showed complete response. No patients required prolonged hospitalization due to poor efficacy. In a prospective study, Klastersky *et al.* proved that treatment with oral antibacterial agents was possible for patients with low risk of FN [11]. In the future, we can expect to manage FN in patients receiving treatment for ovarian cancer with outpatient care using oral antibacterial agents, resulting in improvements in patients' QOL and medical economics.

Although it is important to identify the pathogenic bacteria when administering antibiotic therapy, the positive identification rate is as low as 10% [10]. In the present study, the identification rate via blood cultures was 8.3%, approximately equivalent to previous reports. However, the rate increased to a high level of 23.1% when including urine cultures and cultured vaginal discharge. From the viewpoint of infection control, it is important to identify pathogenic bacteria early using urine and vaginal discharge culture, in addition to blood cultures. Bacteria could be detected in three patients in this study, and in all cases, the pathogen was *E. coli*. Houges *et al.* reported that 60%–70% of pathogenic bacteria causing FN are gram-positive bacteria [13], and therefore infection by gram-negative bacteria such as *E. coli* is relatively rare. At present, there is no report that the pathogenic bacterium of FN associated with ovarian cancer treatment is often *E. coli.* This causal relationship is unclear and should be examined in a larger patient group.

Primary prophylaxis with G-CSF in chemotherapy for epithelial ovarian cancer appears to be of low value in terms of its relationship to the incidence of FN and prognosis, as well as from a medical economic viewpoint. In particular, the occurrence of FN deserves special attention in patients with recurrence, with poor PS, and advanced cancer. However, such patients might be managed with oral antibacterial agents in outpatient care.

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Address reprint requests to:
T. MORI, M.D.
Department of Obstetrics and Gynecology
Kyoto Prefectural University of Medicine
465 Kajii-cho, Kawaramachi Hirokoji
Kamigyo-ku, Kyoto 602-8566 (Japan)
e-mail: moriman@koto.kpu-m.ac.jp