Hiroshima J. Med. Sci.
Vol.44, No.4, 99～103, December, 1995
HIJM 44–16

Clinical Evaluation of Human Granulocyte Colony-stimulating Factor in Chemotherapy for Ovarian Cancer

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ABSTRACT

The clinical evaluation of human granulocyte colony-stimulating factor (G-CSF) in 38 patients treated with chemotherapy for ovarian cancer stage III was investigated among 3 groups. G-CSF was not given in group A (19 courses), was administered from day 5 of chemotherapy in group B (53 courses), and was given when the WBC count decreased to below 2,000/mm^3 in group C (29 courses).

The time to nadir was significantly shorter in group B compared with groups A and C and revealed 10 days for the WBC count and 11 days for the neutrophil count ($p<0.01$), with mean nadir values of 2,896/mm^3 and 982/mm^3 respectively, and so the count of WBC and neutrophil have been kept during the course. The effect of G-CSF was not modified by age, body weight or the number of chemotherapy courses in groups B and C. These results demonstrate that early treatment with G-CSF may allow increased intensity of chemotherapy by using greater doses or by shortening of the interval between cycles.

***Key words**: G-CSF, Ovarian cancer, Chemotherapy*

Ovarian cancer in the advanced clinical stage can now be treated by surgery followed by multiagent chemotherapy based on cisplatin, a development which has improved the prognosis for ovarian cancer in recent years[1,3)]. However, most chemotherapy agents have toxic side effects, limiting the dose that can be given. Leukopenia, resulting from the effect on the bone marrow with its rapid cell turnover, is an important side effect because the patient's resistance to infection is reduced, and is usually avoided by decreasing the chemotherapy dose or extending the administration interval. However, this reduces the effectiveness of the chemotherapy.

Human granulocyte colony-stimulating factor (G-CSF) is a glycoprotein with a molecular weight of 19,000 which was cloned in 1986 from a cell line derived from G-CSF-producing human oral cancer or human bladder cancer. G-CSF has been clinically applied to increase neutrophil levels under various circumstances[10,12)]. We used G-CSF as part of a chemotherapy regimen for ovarian cancer to investigate the efficacy and safety of this agent.

MATERIALS AND METHODS

This study included 38 patients with ovarian cancer stage III who were treated at the Department of Obstetrics and Gynecology at Hiroshima University School of Medicine and related institutions from March 1992 to February 1994. The inclusion criteria for this study are shown in Table 1. Epithelial ovarian cancer was treated using cisplatin-adriamycin-cyclophosphamide (CAP) therapy with 50 – 70 mg/m^2 cisplatin (CDDP), 40 – 60 mg/m^2 adriamycin (ADM), and 500 mg/m^2 cyclophosphamide (CPA). Germ cell tumors and borderline malignancies were treated by a chemotherapy regimen based on CAP therapy.

The patients were divided into 3 groups. Group

Table 1. Inclusion criteria

1)	Histologically confirmed ovarian cancer or suspected ovarian cancer based on cytodiagnosis.
2)	Performance status (PS) of 0–3.
3)	Neutrophil count below 1,000/mm^3 (or a WBC count below 2,000/mm^3).
4)	Adequate organ function.
5)	Age above 15 years.
6)	No serious complications such as pneumonia or hemorrhage.
7)	No history of significant allergy.

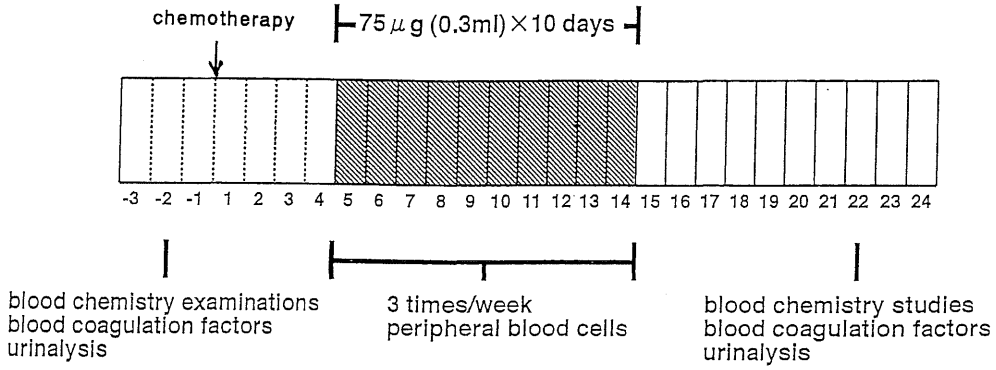

Fig. 1. Administration schedule for G-CSF

A was the control group who received only the above therapy. Group B additionally received 75 μg (0.5 ml) G-CSF once daily for 10 days from day 5 of the chemotherapy regimen (Fig. 1). When the white blood cell (WBC) count increased to above 10,000/mm^3, G-CSF was given on alternate days. Group C received G-CSF only if the WBC count decreased to below 2,000/mm^3.

Blood chemistry examinations were performed immediately before chemotherapy, during G-CSF treatment, and immediately after the completion of G-CSF treatment. Examinations included hematological examination (WBC, RBC, Hb, Ht, platelet), liver and renal function and electrolytes, blood coagulation factors (PT, PTT, fibrinogen, and FDP), and urinalysis. Medications which could mask the effect of G-CSF were restricted during the study period as far as possible, including (1) anti-leukopenia agents (cepharanthin, adenine, inosine, adrenochrome guanylhydrazone mesilate, cytochrome C, lithium carbonate, calcium folinate (Leucovorin), etc.), (2) other CSF preparations, and (3) leukocyte transfusion.

G-CSF administration was discontinued under any of the following circumstances: (1) the WBC count remained above 10,000/mm^3 even after the G-CSF regimen was changed to the alternate day basis, (2) occurrence of clinically significant adverse reactions, and (3) if the attending physician considered discontinuation necessary.

Statistical analysis was performed using the U-test and analysis of variance (Anova).

RESULTS

Background data for the 38 patients are shown in Table 2. Their ages varied widely from 16 to 72 years (mean 54.1 years). The histological diagnosis was epithelial ovarian cancer in 31 of the 38 patients. Adjuvant therapy in addition to G-CSF was performed in 14 patients, as specified in Table 2. The chemotherapy regimens used are listed in Table 3. CAP therapy (CPA + ADM + CDDP) or some modification of CAP therapy was given to 30 of the 38 patients.

Table 2. Background data of the patients

Age	16–72 years old (mean ± SD 54.1 ± 12.9)	
	<20	2
	20–29	1
	30–39	1
	40–49	5
	50–59	12
	60–69	15
	>70	2
Diagnosis	epithelial ovarian cancer	31
	germ cell tumor	3
	borderline malignancy	2
	other lesions (mixed mesodermal tumor)	1
Adjuvant therapy		
	not performed	24
	performed	14
	transfusion	9
	packed red cells	
	platelets	
	antibiotics	5

Table 3. Chemotherapy regimens

CPA	+ ADM	+ CDDP	16
CPA	+ THP	+ CDDP	10
CPA	+ epi-ADM	+ CDDP	4
CPA	+ CBDCA		2
VP16	+ CBDCA		2
PEP	+ VBL	+ CDDP	2
CPA	+ VBL	+ CDDP	1
CPA	+ THP	+ CBDCA	1

Changes in the WBC and neutrophil counts in groups A, B, and C after the commencement of

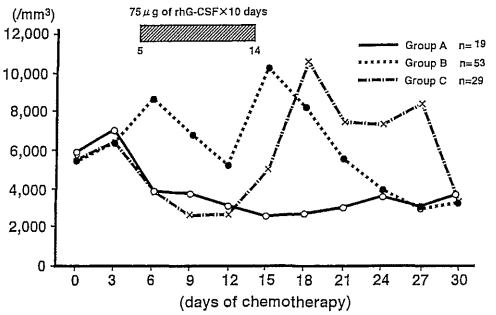

Fig. 2. Changes in the WBC count

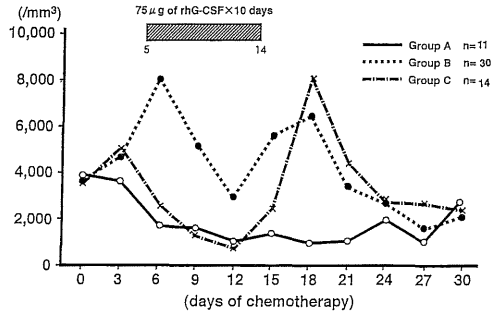

Fig. 3. Changes in the neutrophil count

chemotherapy are shown in Figs. 2 and 3, respectively. The mean nadir values of the WBC and neutrophil counts are given Tables 4 and 5. In group A (control), the time between the commencement of chemotherapy and the nadir, respectively was 15 days for the WBC count and 16 days for the neutrophil count, with the mean nadir values of 2,226/mm^3 and 680/mm^3, respectively. In group B, the time to nadir was significantly shorter at 10 days for the WBC count and 11 days for the the neutrophil count ($p<0.01$), with mean nadir values of 2,896/mm^3 and 982/mm^3, respectively. In group C, the occurrence of the nadir of the WBC and neutrophil count before G-CSF treatment was similar to group A,

Table 4. Characteristics of the nadir WBC count and nadir WBC counts in the 3 groups

Group	No. of courses	Mean days until nadir	Nadir count mean	Nadir count SD
Group A	19	15 *	2,226	851
Group B	53	10 **	2,896	1,607 *
Group C	29	12	1,690	610

*p<0.01 (Anova)
**p<0.05

Table 5. Characteristics of the nadir neutrophil count and nadir neutrophil counts in the 3 groups

Group	No. of courses	Mean days until nadir	Nadir count mean	Nadir count SD
Group A	11	16 *	680	402
Group B	30	11	982	666
Group C	14	13	630	382

*p<0.01 (Anova)

and the mean nadir values were close to those in group A. The WBC count was significantly lower in group C ($p<0.01$) than in group B.

According to the grading of WHO, leukopenia of grade 3 or worse occurred in 9 out of 19 courses of chemotherapy (47.4%) in group A, in 16 out of 53 courses (30.2%) in group B, and in 21 out of 29 courses (72.4%) in group C (Table 6). The incidence of severe leukopenia was lowest in group B and highest in group C.

The RBC count and platelet count were higher in group A than in the other 2 groups, but there were no significant differences between the groups, indicating that G-CSF treatment had no effect on RBC or platelet counts.

The correlations between the nadir WBC count or the time to nadir and various patient background factors, including age, number of chemotherapy courses, and weight (Fig. 4), were assessed. Comparison between patients aged

Table 6. Grade of leukopenia

	Total no. of courses	Grades of leukopenia				
		grade 4	grade 3	grade 2	grade 1	grade 0
Overall	116	9	46	33	13	12
	100.0	8.0	40.7	29.2	11.5	10.6
Group A	19	1	8	5	5	—
	100.0	5.3	42.1	26.3	26.3	—
Group B	53	2	14	19	8	10
	100.0	3.8	26.4	35.8	15.1	18.9
Group C	29	3	18	8	—	—
	100.0	10.3	62.1	27.6	—	—

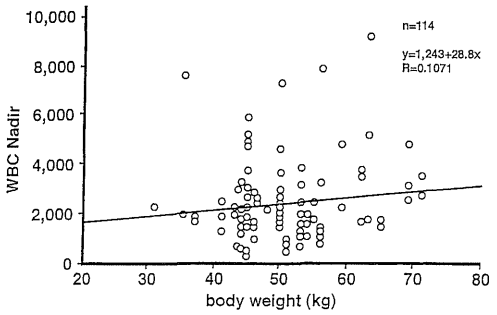

Fig. 4. Correlation between nadir values and body weight

above and below 60 years in each group revealed no significant difference in either the nadir WBC count or the time to nadir. Comparison between the patients receiving 5 or more courses of chemotherapy and less than 5 courses in each group also revealed no significant difference in the nadir WBC count or the time to nadir. Furthermore, there was no correlation between body weight and the nadir WBC count.

G-CSF treatment caused an adverse reaction in only 1 patient, who developed low back pain. No patient developed infection and no abnormalities were found in blood chemistry studies, blood coagulation factors, or urinalysis.

DISCUSSION

The prognosis for ovarian cancer has improved since the introduction of cisplatin chemotherapy. Cisplatin alone achieves a cure rate of about 30%, while multiple-drug chemotherapy generally improves the outcome[1]. In addition, increasing the dose can improve the cure rate[6,9,13] and extend the mean survival time[7]. Antitumor agents such as cisplatin affect not only cancer cells but also normal cells and thus damage organs with a rapid cell turnover. The bone marrow is one of the organs most prone to damage by chemotherapy, and bone marrow depression is a dose-limiting factor for most antitumor agents. Chemotherapy-associated bone marrow dysfunctions include leukopenia, thrombocytopenia, and erythropenia. Since the lifespan of white blood cells is particularly short at 8 days, leukopenia occurs in the early stage of chemotherapy. Leukopenia is also important because it increases the host's susceptibility to infection.

The development of recombinant human G-CSF has dramatically improved the treatment of leukopenia and neutropenia due to bone marrow depression. G-CSF acts on granulocyte precursor cells (CFU-G) to promote differentiation, growth, and maturation as well as enhancing their function[2]. G-CSF also enhances IL-3 dependent proliferation of hematopoietic progenitors[5].

The present study assessed the clinical effect of G-CSF in patients treated with chemotherapy for ovarian cancer. G-CSF was not given in group A, was administered from day 5 of chemotherapy in group B, and was given when the WBC count decreased to below 2,000/mm^3 in group C. The nadir WBC and neutrophil counts increased prominently and the time until nadir was also shortened in group B compared with groups A and C. These results demonstrate that chemotherapy-related bone marrow dysfunction can be prevented by using G-CSF from day 5 of chemotherapy.

Morstyn et al[8] reported that the nadir WBC and neutrophil counts were not increased when G-CSF was administered before chemotherapy. In contrast, when G-CSF was administrated at 1 day after chemotherapy, the counts increased so sharply that neutrophil dysfunction and hyperviscosity were possible. They also reported that the nadir WBC and neutrophil counts were increased when G-CSF was administrated from day 7 of chemotherapy, suggesting the usefulness of G-CSF administration starting from this time. In our study, leukopenia and neutropenia were effectively prevented by G-CSF administration from day 5 of chemotherapy. We also found that grade 3 or worse leukopenia was less frequent in group B. Therefore, we consider that the use of G-CSF in the early stage of chemotherapy is a useful method to prevent bone marrow depression.

Analysis of the patients by age and by the number of chemotherapy courses was used to identify any correlations between these factors and the changes in the WBC and neutrophil counts, because there might be differences in the response to G-CSF or the deterioration of bone marrow function. However, no statistically significant differences were found in the changes of the WBC and neutrophil counts between these subgroups in all 3 patient groups, indicating that the effect of G-CSF was not modified by age or the number of chemotherapy courses. However, the chemotherapy regimen may be changed for the elderly or for patients undergoing repeated courses, including a decrease in dosage, so G-CSF therapy should also be changed accordingly while monitoring the response. Since there was no difference in the effect of G-CSF (75 μg once a day) based on body weight, this dose may be the optimum dose. However, it has been suggested that the prophylactic effect of G-CSF against bone marrow depression is improved by increasing the dose[4,11], so further investigation appears necessary.

In conclusion, in G-CSF administration commenced at an early stage chemotherapy increased the nadir leukocyte and neutrophil counts and shortened the time to nadir. Early treatment with G-CSF may allow increased intensity of chemotherapy by using greater doses or by shortening of the interval between cycles.

ACKNOWLEDGMENT

We wish to thank Dr. Atsushi FUJIWARA, Dr. Masanori UEDA, Dr. Yukinori NAKAO, Dr. Masaki HORIKAWA, Dr. Yoshimitsu KURIMURA, Dr. Densho KOH and Dr. Shingo KAWAMURA of the study group for Hiroshima Hematopoietic Factors.

(Received July 31, 1995)
(Accepted November 6, 1995)

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