Granulocyte-Colony Stimulating Factors for Secondary Prevention of Leucopenia in Patients Receiving Chemotherapy

Jariya Lowathanasirikul MD*, Sumonmal Manusirivithaya MD*,
Siriwan Tangjitgamol MD*, Surawute Leelahakorn MD*

** Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hospital*

Objective: *To evaluate the effectiveness of GCSF as a secondary preventive adjunct to chemotherapy in the gynaecologic cancer patients who previously had grade 3-4 neutropenia or leucopenia from chemotherapy.*
Material and Method: *We retrospectively reviewed the medical records of 94 chemotherapeutic cycles with GCSF as secondary prophylaxis in 29 patients with gynaecologic malignancy between January 1996 and April 2005.*
Results: *The median age of the patients was 51 years (21-75). Most of the patients had ovarian cancers (19 cases, 65.6%). From secondary GCSF, grade 4 neutropenia was developed in 12 of 94 cycles (12.8%), and grade 4 leucopenia was developed in 5 of 94 cycles (5.3%). There were no patients developing febrile neutropenia after GCSF support.*
Conclusion: *Secondary GCSF prophylaxis was effective in preventing grade 4 leucopenia, grade 4 neutropenia, and febrile neutropenia.*

Keywords: *Secondary GCSFs prophylaxis, Neutropenia, Leucopenia, Chemotherapy*

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Systemic anti-cancer chemotherapy has the cytotoxic effect to both tumor cells and normal dividing cells. The magnitude of myelosupression depends on type and intensity of chemotherapy administered[1]. Neutropenia is a major factor contributing to infection, morbidity, and mortality in patients undergoing chemotherapy for cancer[1].

The risk of infection is directly related to the duration and degree of neutropenia. Patients with grade 4 neutropenia for more than 5 days are at high risk of severe infection[2]. Fever in the setting of neutropenia generally leads to hospitalization for evaluation and administration of empiric broad-spectrum antibiotics and antifungals until resolutions of fever, haematological recovery and eradication of pathogenic bacteria in case of documented infection. Febrile neutropenia is also associated with delay in chemotherapy cycles or reduction of chemotherapy doses as well as reduce quality of life and quickly develop into life-threatening situation in patients undergoing treatment for cancer, which should increase financial burden to both patients and medical system[2].

Overall, the mortality rate associated with febrile neutropenia is in range of 0-3% in patients with solid tumor[3]. Prophylaxis against chemotherapy-induced neutropenia can be done by decreased chemotherapeutic doses relevant to grading of previous leucopenia and neutropenia. Another method is to increase interval between chemotherapy courses until white blood cells and neutrophils return to normal range. Thus, the presence of chemotherapy-induced neutropenia can often result in a reduction in the chemotherapy dose or a delay in starting the next chemotherapy cycle. These practice certainly had negative impact on treatment outcomes[4].

Granulocyte-Colony Stimulating Factors (GCSF) are glycoproteins that regulate the proliferation of bone marrow progenitor cells and their matura-

Correspondence to : Lowathanasirikul J, Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hospital, Bangkok 10300, Thailand. E-mail: jariya_gift@yahoo.com

tion into fully differentiated circulating blood cells[5]. Human GCSF also enhances the functional properties of mature cells by increasing phagocytotic activity, anti-microbial-killing and antibody-dependent cell-mediated cytotoxicity[5]. When administered as a preventive adjunct to chemotherapy, GCSF have shown in clinical trials to shorten the neutropenic period and to reduce the incidence of febrile neutropenia in high-risk patients[6-8]. The American Society of Clinical Oncology (ASCO) recommends the prophylactic use of GCSF for patients who receive standard doses of chemotherapy including primary and secondary prophylaxis of febrile neutropenia[9,10]. Primary prophylaxis refers to use of the growth factor before there would be any occurrence of neutropenia[9,10]. Secondary prophylaxis refers to its use in subsequent chemotherapy cycles after the occurrence of neutropenia in at least one of the preceding cycles[9,10].

Generally, primary prophylaxis of febrile neutropenia may not be feasible, because it is difficult to identify in whom grade 4 neutropenia and leucopenia would occur, or by which chemotherapeutic agents. The current guidelines of ASCO recommend the use of a hematopoietic growth factor as secondary prophylaxis[9].

The purpose of this study was to evaluate the effectiveness of GCSF as a secondary preventive adjunct to chemotherapy in the treatment of patients with gynaecologic cancers. Another objective is to evaluate whether there are any factors associated with the effectiveness of GCSF.

Material and Method

This study was conducted after the approval from the Ethics Committees of our institution. The patients who received GCSF as secondary prophylaxis at the Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hospital, between January 1996 and April 2005 were identified.

Generally in our institution, GCSF (as a secondary prophylaxis) was administered for duration of about 5 days (or less if the white cell count is over 30,000 cell/mm^3 or absolute neutrophil is over 15,000/mm^3), starting at the fourth to seventh day after the first day of chemotherapy. The patients usually had complete blood cell counts with differential leukocyte counts evaluated every 2-4 days from start of GCSF until after their nadir.

Data were considered ineligible if GCSF were given for less than 3 days, or had blood cell counts with differential leukocyte counts less than 5 times in each course.

Grading of neutropenia and leucopenia were classified according to WHO grading system[4]. Grade 0, 1, 2, 3, and 4 neutropenia were referred to absolute neutrophil count $\geq$ 2,000/mm^3; 1,500-1,999/mm^3; 1,000-1,499/mm^3; 500-999/mm^3; and less than 500/mm^3 respectively. Grade 0, 1, 2, 3, and 4 leucopenia was referred to white blood cell count $\geq$ 4,000/mm^3; 3,000- 3,999/mm^3; 2,000-2,999/mm^3;1,000-1,999/mm^3; and less than 1,000/mm^3 respectively. Fever was defined when the body temperature is above 100.4°F (38°C.), while febrile neutropenia was defined when a temperature was more than 38.3°C (101°F) on several occasions with neutrophils count is < 500/mm^3 or is expected to fall to that level within 1-2 days[11].

Data collected were clinical data of the patients, status of cancer, chemotherapeutic regimen, type of GCSF, incidence and duration of grade 3 and 4 neutropenia, leucopenia, febrile neutropenia, and next chemotherapeutic cycle, whether it can be administered at the same dose and schedule.

Data were analyzed by parametric and non-parametric statistics using SPSS statistical software version 11.5 (Chicago, IL). Descriptive statistics were used for demographic data and summarized as mean with standard deviation (SD) or median with range. Categorized variables were compared with the Chi-squared test or Fisher's exact test as appropriate. Differences between continuous variables were evaluated with Mann-Whitney U test. p-value $\leq$ 0.05 was considered as statistical significance.

Results

Ninety-four chemotherapeutic cycles with secondary GCSF prophylaxis from 29 patients with gynecologic malignancies were eligible for the study. Median age of the patients was 51 years (21-75 years). The distribution of cancer types were ovarian cancer 19 cases (65.6%), cervical cancer five cases (17.2%), and uterine cancer five cases (17.2%). Two patients (6.9%) had previously received radiotherapy.

The median number of courses of chemotherapy with secondary GCSF prophylaxis evaluated in each patient was three courses (1-9 courses). Two patients had secondary GCSF prophylaxis evaluated from 2 regimens of chemotherapy; the rest had been evaluated for 1 chemotherapeutic regimen.

From all 94 courses, all had previous grade 3-4 neutropenia with 86 courses (91.5%) with previously grade 4 neutropenia. The median lowest neutrophils

before these courses were 215/mm^3 (36-810/mm^3), and the median lowest white blood cell was 1,600/mm^3 (240-3,070/mm^3).

Chemotherapeutic regimens employed with secondary GCSF were demonstrated in Table 1. Paclitaxel in combination with carboplatin were the most common seen with secondary GCSF prophylaxis, 30 courses (31.6%), followed by cisplatin and ifosfamide, 16 courses (16.8%); single agent paclitaxel 13 courses (13.7%); cisplatin and cyclophosphamide 11 courses (11.5%); cisplatin, etoposide, and bleomycin 9 courses (10.5%).

Type of GCSF used in these patients was filgrastim in almost all courses, while lenograstim were given in two courses. GCSF was given for five days in almost all courses (92 courses, 97.9%), and it was given for six and seven days, each for one course.

Nadir of neutrophil and white blood cell count in 94 chemotherapeutic cycles with secondary prophylatic GCSF were shown in Table 2. Grade 3 and 4 neutropenia were evidenced in 25 and 12 of 94 cycles (26.6% and 12.8%). Grade 3 and 4 leucopenia developed in 13 and 5 cycles (13.8% and 5.3%). The median duration of grade 4 neutropenia and leucopenia was equal at only 1 day.

There was no event of febrile neutropenia in any cycle of secondary prophylactic GCSF in this study. However, fever higher than 38∞C was presented in 7 of 94 cycles (7.4%), not all of these were associated with neutropenia. Infections were documented in 5 cycles (5.3%), all were diagnosed as upper urinary tract infection (UTI). Antibiotic therapies were used in 6 cycles, 5 in cases of UTI, another one was used in patient who had fever with neutrophilia and leucocytosis, but no definite evidence of infection. The median duration of antibiotic use was 7 days (1-13 days). The median duration of fever was 2 days (1-3 days). The delay of chemotherapy between treatment cycles occurred in 7 of 94 cycles (7.4%). The median duration of the delayed cycle was 7 days (2-10 days). The reduc-

Table 1. Number and percentages of GCSF given according to the type of chemotherapy (N = 94 courses)

Regimen of chemotherapy	Number (Cycles)	%
Paclitaxel and carboplatin	30	31.9%
Cisplatin and ifosfamide	16	17.1%
Paclitaxel	13	13.8%
Cisplatin and cyclophosphamide	11	11.7%
Cisplatin, etoposide, and bleomycin	9	9.6%
Cisplatin and etoposide	5	5.3%
Cisplatin and 5-FU	4	4.3%
Cisplatin and adriamycin	3	3.2%
Carboplatin and cyclophosphamide	2	2.1%
Cisplatin, cyclophosphamide, and adriamycin	1	1.0%

Table 2. Results of prophylactic GCSF in terms of nadir leukocyte and neutrophil and duration of leucopenia and neutropenia (N = 94 courses)

Hematologic profile	Leucopenia Number (%)	Neutropenia Number (%)
grade 0	26 (27.7%)	30 (31.9%)
grade 1	22 (23.4%)	16 (17.0%)
grade 2	28 (29.8%)	11 (11.7%)
grade 3	13 (13.8%)	25 (26.6%)
grade 4	5 (5.3%)	12 (12.8%)
Median (range) duration of grade 3-4(days)*	3 (1-6)	1 (1-9)
Median (range) duration of grade 4(days)**	1 (1-6)	1 (1-5)

* considered only those who had experience ≥ grade 3 leucopenia or neutropenia
** considered only those who had experience grade 4 leucopenia or neutropenia

tion of chemotherapeutic dose in the next cycle occurred in 5 of 94 cycles (5.3%). In this study, next cycle of chemotherapy can be achieved on schedule without dose reduction in 87 cycles (92.5%).

Age, chemotherapeutic regimens, type of cancer, white blood count, and absolute neutrophil count before chemotherapy, and previous lowest neutrophil and white blood count were analyzed for possible association with grade 3-4 neutropenia in cycle with secondary GCSF prophylaxis. We found that patients of more than 50 years had higher rate of grade 3-4 neutropenia compared to those with younger age (47.4% vs 27.0%, p = 0.049). Patients with uterine cancer had 76.9% of grade 3-4 neutropenia compared to of cervical cancer (50%) and of ovarian cancer (29.2%) (p = 0.004). Chemotherapeutic regimens also had influenced on grade 3-4 neutropenia. Regimens that provided nearly or over 50% rate of grade 3-4 neutropenia were regimens containing etoposide, ifosfamide, and adriamycin (Table 3). White blood count and absolute neutrophil count before starting chemotherapy, and previous lowest neutrophil and white blood count showed no association with grade 3-4 neutropenia in cycle with secondary GCSF prophylaxis (Table 4).

Concerning side effect from the use of prophylactic GCSF, bone pain was recorded in 23 of 94 cycles (24.5%). Mild or moderate pain, which did not require analgesics or required only acetaminophen, was noted in 17 cycles (18.1%). Pain that required analgesics other than acetaminophen were noted in 6 cycles (6.4%). No one had to discontinue GCSF because of their bone pain.

Regarding, the overstimulation of neutrophil and white blood cell, the median of highest white blood cell levels after prophylactic GCSF was 15,400/mm^3 (2,900-63,100/mm^3) and the median of highest neutrophil levels was 12,789/mm^3 (1,395- 57,960/mm^3). There were 13 cycles in which white blood cell levels exceeded 30,000/mm^3(14.3%), and 36 cycles in which neutrophil exceeded 15,000/mm^3(39.6%).

Table 3. Association between patients characteristics, type of cancer, type of chemotherapy and grade 3-4 neutropenia in patients receiving secondary GCSFs prophylaxis (N = 94 courses)

	Neutropenia		p-value*
	Grade 1-2	Grade3-4	
Age (years)			0.049*
< 50 (n = 37)	27 (73.0%)	10 (27.0%)	
> 50 (n = 57)	30 (52.6%)	27 (47.4%)	
Type of cancer			0.003*
Ovary (n = 65)	46 (70.8%)	19 (29.2%)	
Cervix (n = 16)	8 (50.0%)	8 (50%)	
Uterus (n = 13)	3 (23.1%)	10 (76.9%)	
Type of chemotherapy			0.004**
Regimens with etoposide, ifosfamide, and adriamycin	14 (14.9%)	20 (21.3%)	
Cisplatin-etoposide	2 (40.0%)	3 (60.0%)	
Cisplatin-etoposide-bleomycin	5 (55.6%)	4 (44.4%)	
Cisplatin-ifosfamide	6 (37.5%)	10 (62.5%)	
Carboplatin-cyclophosphamide-adriamycin	1 (100.0%)	0 (0.0%)	
Cisplatin-adriamycin	0 0.0%)	3 (100%)	
Other regimens	43 (45.7%)	17 (18.1%)	
Paclitaxel	10 (76.9%)	3 (23.1%)	
Paclitaxel-carboplatin	20 (66.7%)	10 (33.3%)	
Cisplatin-cyclophosphamide	8 (72.7%)	3 (27.3%)	
Carboplatin-cyclophosphamide	2 (100.0%)	0 (0.0%)	
Cisplatin-5-FU	3 (75.0%)	1 (25%)	
Total	57 (60.6%)	37 (39.4)	

* p-value by Chi-square

** p-value compared between ovarian cancer vs cervical/uterine cancers

*** p-value compared between regimen with etoposide, ifosfamide, adriamycin vs other regimens

Table 4. Comparing previous hematologic profile in patients with and without grade 3-4 neutropenia in patients receiving secondary GCSFs (N = 94 courses)

	Neutropenia		p-value*
	Grade 1-2 (N = 57)	Grade 3-4 (N = 37)	
Lowest leucocyte count from all previous courses	5,200 (3,000-17,900)	4,800 (3,100-11,300)	0.640
Lowest neutrophil count from all previous courses	2,896 (1,020-9,555)	3,300 (1,453-9,718)	0.899
Leucocyte count before chemotherapy	5,000 (3,000-17,900)	5,200 (3,000-11,300)	0.747
Neutrophil count before chemotherapy	2,852 (1,534-9,555)	3,216 (1,020-9,718)	0.286

Reported as median (range)
* p-value by Mann-Whitney U test

Discussion

Myelosuppressive chemotherapy is frequently complicated by neutropenic fever. Because of the risk of severe morbidity and mortality, clinical practice is to postpone chemotherapy cycles or to reduce the dose in order to prevent (cumulative) toxicity. It has been shown that dose reduction of chemotherapy is associated with a lower response rate and a relatively poor overall survival[4]. Some study had suggested that GCSF improves the adherence to the chemotherapy schedule and minimizes dose modifications in elderly patients receiving chemotherapy[12]. Therefore, prophylactic treatment with GCSF has been considered in clinical practice for these patients.

This study was designed to evaluate whether prophylactic administration of GCSF may indeed prevent hematologic complications in patients with history of grade 3-4 neutropenia after myelosuppressive chemotherapy. In our study, prophylactic GCSF can prevent grade 3-4 neutropenia in 57 of 94 cycles (67.6%) and prevent grade 4 neutropenia in 82 of 94 cycles (87.2%). Moreover, none had febrile neutropenia under secondary GCSF prophylaxis. Some randomized clinical trial had documented that the risk of febrile neutropenia may be reduced substantially by primary prophylaxis with GCSF, when the risk of febrile neutropenia without GCSF is approximately 20%[13].

Several risk factors associated with development of chemotherapy-induced neutropenia include age[14], performance status[15], medical comorbidities[16], laboratory abnormalities[15], and tumor types[16]. Elderly patients tend to have more limited hematopoietic reserve than younger patients do, and are therefore more susceptible to chemotherapy-induced myelosuppression than younger patients are[17]. This was confirmed by our study that patients of over 50 years had statistically significant higher rate of developing grade 3-4 neutropenia in spite of prophylactic GCSF ($p = 0.049$). White blood cell levels and neutrophil levels before chemotherapy had no significant association with incidence of grade 3-4 neutropenia.

Each chemotherapy was known to have different myelosuppressive activities[1]. Those with high myelosuppressive activity also tend to provide grade 3-4 neutropenia despite prophylactic GCSF. From our study, regimens containing etoposide, ifosfamide, and adriamycin had higher chance of grade 3-4 neutropenia although prophylactic GCSF was given.

Concerning tumor types and the risk of grade 3-4 neutropenia, in our study, cervical and uterine cancers were statistically significant in association with higher incidence of grade 3-4 neutropenia. These may be due to the regimens of chemotherapy used in these patients. Four of 16 chemotherapeutic cycles (25%) of cervical cancers were cisplatin and etoposide, and three were cisplatin and ifosfamide. In uterine cancers, 6 of 13 cycles (46.2%) were cisplatin and ifosfamide, while 3 of 13 cycles (23.1%) were used cisplatin and adriamycin. Hence, the type of tumor may not be directly associated with neutropenia, but with the chemotherapy used in that cycle.

Regarding the side effects of prophylactic GCSF, bone pain was recorded in 23 of 94 cycles (24.5%). Moderate pain which acetaminophen could control the symptom was noted in 17 of 94 cycles (18.1%), and pain which required analgesics other than acetaminophen was noted in 6 cycles (6.4%). No patients discontinued the use of GCSF because of intolerable pain. The frequency of this side effect was comparable to other studies. In Vogel et al's study, mild to moderate medullary bone pain from the use of GCSF was about 30% and severe bone pain was 2%[13]. In the meta-analysis of prophylactic GCSF, the mean frequency of complaints of bone pain among patients receiving

growth factor was 21% (17-25%)[18].

In conclusion, secondary prophylaxis GCSF was effective in preventing grade 4 leucopenia, grade 4 neutropenia, and febrile neutropenia. However, the effectiveness was less in elderly patients and in those who received specific, high myelosuppressive chemotherapy.

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การใช้ Granulocyte-Colony Stimulating Factors เพื่อป้องกันแบบทุติยภูมิต่อการเกิดภาวะเม็ดเลือดขาวต่ำในผู้ป่วยที่ได้รับเคมีบำบัด

จริยา หล่อวัฒนศิริกุล, สุมนมาลย์ มนัสศิริวิทยา, ศิริวรรณ ตั้งจิตกมล, สุรวุฒิ ลีฬหากร

วัตถุประสงค์: *เพื่อศึกษาผลของ Granulocyte-colony stimulating factors (GCSF) ที่ให้แบบทุติยภูมิเพื่อป้องกันการเกิดภาวะเม็ดเลือดขาวต่ำ ในผู้ป่วยมะเร็งนรีเวชที่เคยเกิด grade 3-4 neutropenia หรือ leucopenia จากเคมีบำบัด*

วัสดุและวิธีการ: *ทำการศึกษาเชิงพรรณนาแบบย้อนหลังโดยเก็บข้อมูลจากเวชระเบียนผู้ป่วยนอก แฟ้มประวัติผู้ป่วยใน และแฟ้มประวัติการให้เคมีบำบัดทั้งหมด 94 ครั้ง ในผู้ป่วย 29 คนที่เข้ารับการรักษาในแผนกมะเร็งนรีเวช และได้รับ GCSF เพื่อป้องกันการเกิดภาวะเม็ดเลือดขาวต่ำแบบทุติยภูมิ ในวิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาลตั้งแต่เดือนมกราคม พ.ศ. 2539 จนถึงเดือนเมษายน พ.ศ. 2548*

ผลการศึกษา: *จากการศึกษาเวชระเบียนของผู้ป่วยที่ได้รับ GCSF หลังได้รับเคมีบำบัดพบว่ามัธยฐานอายุของผู้ป่วย 51 ปี (21-75 ปี) พบเป็นมะเร็งรังไข่มากที่สุด (ร้อยละ 65.6) หลังการให้ GCSF พบอัตราการเกิด grade 4 neutropenia ร้อยละ12.8, grade 4 leucopenia ร้อยละ 5.3 และไม่พบการเกิด febrile neutropenia หลังได้รับ GCSF*

สรุป: *การให้ GCSF เพื่อป้องกันการเกิดเม็ดเลือดขาวต่ำแบบทุติยภูมิมีประสิทธิภาพในการป้องกันการเกิด grade 4 neutropenia, grade 4 leucopenia, และ febrile neutropenia*