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Research article

Prescribing Patterns of Myeloid Growth Factors to Prevent Chemotherapy Related Febrile Neutropenia in Cancer Patients

Winita Rodhetbhai[1,2], Krittika Tanyasaensook[1], Usa Chaikledkaew[1]

[1]Department of Pharmacy, Faculty of Pharmacy, Mahidol University
[2]Department of Pharmacy, Faculty of Medicine Vajira Hospital, Bangkok

Abstract

Objective: To explores the patterns of myeloid growth factors (MGFs) usage in the prevention of chemotherapy (CMT) induced neutropenia. **Method:** This study was a retrospective chart review study. Data from 192 patients with 1,058 CMT cycles from 17 different cancer types were collected between January 1 and June 30, 2015. Risk assessment of febrile neutropenia (FN) was performed prior to every CMT cycle. The patterns of MGFs use for prophylaxis were recorded. **Results:** Overall, the consistency of the MGFs prophylaxis pattern with the Guideline was 63.04% of drug use. No CMT cycles were in the 'Overuse' group. Amongst the CMT regimens with FN high risk, 67.57% of the MGFs prophylaxis were consistent with the Guideline. Non-Hodgkin lymphoma was the most cancer type that received the MGFs prophylaxis. The majority of the MGFs prophylaxis in the CMT regimen with intermediate risk for FN and additional patient risk factors was in the 'Underuse' group (89.21%). Overall, MGFs prophylaxis was prescribed in 76 cycles (50 cycles for primary prophylaxis, and 26 cycles for secondary prophylaxis). Filgrastim was prescribed in all of cycles. The average of MGFs prophylaxis duration were 6.8±1.19 and 6.3±1.67 days for primary prophylaxis and secondary prophylaxis, respectively. **Conclusion:** Primary MGFs prophylaxis was more consistent with the Guideline than the secondary prophylaxis. Most of the CMT regimens with MGFs prophylaxis were classified as high FN risk CMT. Non-Hodgkin lymphoma and sarcoma with a higher reported FN rate, were the cancer types with the greatest adherence to the MGFs prophylaxis guideline.

Keywords: cancer, febrile neutropenia, myeloid growth factors, chemotherapy

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corresponding author: Winita Rodhetbhai, Department of Pharmacy, Faculty of Medicine Vajira Hospital, Bangkok, Thailand 10300 **E-mail**: winita@nmu.ac.th

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บทความวิจัย

รูปแบบการสั่งใช้ยา Myeloid Growth Factors เพื่อป้องกันภาวะนิวโทรฟิลต์ในเลือดต่ำที่มีภาวะไข้ร่วมด้วยจากการใช้ยาเคมีบำบัดในผู้ป่วยมะเร็ง

วินิตา รอดเหตุภัย[1,2], กฤตติกา ตัญญูะแสนสุข[1], อุษา ฉายเกล็ดแก้ว[1]

[1]ภาควิชาเภสัชกรรม คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล

[2]ฝ่ายเภสัชกรรม คณะแพทยศาสตร์วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช กรุงเทพมหานคร

บทคัดย่อ

วัตถุประสงค์: ศึกษารูปแบบการสั่งใช้ยากลุ่ม myeloid growth factors (MGFs) เพื่อป้องกันภาวะนิวโทรฟิลต์ในเลือดต่ำที่มีภาวะไข้ร่วมด้วย (FN) จากการใช้ยาเคมีบำบัดในประเด็นความสอดคล้องและไม่สอดคล้องกับแนวทางปฏิบัติ **วิธีการ:** การศึกษาทบทวนเวชระเบียนแบบย้อนหลังในผู้ป่วย 192 รายที่เป็นมะเร็ง 17 ชนิดและได้รับวงรอบเคมีบำบัดทั้งหมด 1058 ครั้ง การศึกษาเก็บข้อมูลระหว่างวันที่ 1 มกราคม 2558 ถึง 30 มิถุนายน 2558 การประเมินความเสี่ยงของการเกิด FN ทำในทุกวงรอบเคมีบำบัด และบันทึกรูปแบบการสั่งใช้ยากลุ่ม MGFs **ผลการวิจัย**: การใช้ยา MGFs เพื่อป้องกันมีความสอดคล้องกับแนวทางปฏิบัติร้อยละ 63.04 ไม่มีวงรอบที่มีการสั่งใช้ MGFs เกินจากแนวทาง ในวงรอบที่มีการใช้สูตรยาเคมีบำบัดที่จัดอยู่ในประเภทความเสี่ยงสูง พบว่า ร้อยละของความสอดคล้องเท่ากับ 67.57 โดยมะเร็งต่อมน้ำเหลือง (non-Hodgkin lymphoma) มีการใช้ยากลุ่ม MGFs เพื่อป้องกันมากที่สุด ส่วนวงรอบที่มีการใช้สูตรยาเคมีบำบัดที่จัดอยู่ในประเภทความเสี่ยงปานกลางร่วมกับมีปัจจัยเสี่ยงของผู้ป่วยนั้น พบว่ามีความไม่สอดคล้องแบบใช้น้อยกว่าที่กำหนดร้อยละ 89.21 จากจำนวนทั้งหมดมีการใช้ MGFs เพื่อป้องกันใน 76 วงรอบ (การป้องกันปฐมภูมิ 50 วงรอบและการป้องกันทุติยภูมิ 26 วงรอบ) โดยเป็นการสั่งใช้ยา filgrastim ทั้งหมด จำนวนวันเฉลี่ยของการได้รับยา filgrastim เพื่อป้องกันสำหรับการป้องกันปฐมภูมิคือ 6.8 วัน และ 6.3 วันสำหรับการป้องกันทุติยภูมิ **สรุป**: การให้ MGFs เพื่อป้องกันปฐมภูมิมีความสอดคล้องกับแนวทางปฏิบัติมากกว่าการใช้เพื่อป้องกันทุติยภูมิ โดยส่วนใหญ่ของวงรอบที่มีการสั่งใช้ยา MGFs เพื่อป้องกันจัดเป็นสูตรยาเคมีบำบัดที่มีความเสี่ยงสูง มะเร็งชนิด non-Hodgkin lymphoma และ sarcoma มีการสั่งใช้ยา MGFs เพื่อป้องกันสอดคล้องกับแนวทางปฏิบัติมากที่สุด

คำสำคัญ: มะเร็ง นิวโทรฟิลต์ในเลือดต่ำ ยากลุ่ม myeloid growth factors ยาเคมีบำบัด

Introduction

Bone marrow suppression is a serious side effect of chemotherapy (CMT) that results in the reduction of white blood cell, red blood cell and platelet production. The subsequent conditions are called neutropenia, anemia and thrombocytopenia, respectively. Neutrophils are the most abundant human white blood cells that play an important role in the immune response against invading pathogens (1). Therefore, neutropenia, especially febrile neutropenia (FN), can lead to medical emergencies and potential hospitalization where empiric broad-spectrum antibiotics are commonly recommended. Moreover, the occurrence of FN after early CMT cycles may affect subsequent CMT dosage and delay treatment schedule, which would influence the final treatment outcomes (2, 3). The incidence rate of neutropenia is variable depending on cancer types, type of CMT and patient risk factors. A study revealed that the most FN episodes were treated in the inpatient setting (4). The average yearly cost per FN episode is between 13,372 and 20,920 USD in America (2, 3). In Thailand, a study showed the mean cost of hospitalization to be about 76,484 THB (approximately 2,549 USD) (5). FN not only affects hospitalization rate and cost, but also increases the mortality rate, which is about 8.0%, 8.9%, and 14.3% for patients with solid tumors, lymphoma, and leukemia, respectively (3).

Myeloid growth factors (MGFs) is a class of biologic agents developed from granulocyte colony stimulating factor (G-CSF; e.g. filgrastim and pegfilgrastim and granulocyte- macrophage colony stimulating factor (GM-CSF e.g. sargramostim) using human recombinant technique. These two factors are growth factors that normally regulate the proliferation, differentiation, survival, and activation of cells in the myeloid lineage (6). Many studies confirm that MGFs usage can reduce the incidence, duration and severity of FN from CMT (7-10). Moreover, it can also decrease the risks of infection and hospitalization, but has no effect on mortality rate (7-9). Overall, MGFs can reduce the rate of FN by around 50% (8, 9).

In addition, MGFs is costly. Many trials have proved the benefit of MGFs usage in terms of the decrease in hospitalization costs, despite the extra cost of MGFs. However, the magnitude of the benefit varies among studies due to the differences in the cost of care in each country (11-14). Several guidelines from the cancer organization recommends MGFs prophylaxis in situations where the overall FN risk is more than 20%, since this shows potential for maximum cost-effectiveness (15-17). Therefore, FN risk assessment should be performed prior to every CMT cycle. These recommendations were developed based on clinical benefits (15-17). Although the international guidelines strongly recommend the use of MGFs in selected situations, many studies reveal that most circumstances of MGFs usage is inconsistent with the Guidelines, with incidences of misuse, overuse and underuse (18-20). However, such study has never been explored in Thailand yet. Therefore, the aim of this study was to demonstrate MGFs use patterns for the prevention of CMT induced FN at one of the University hospitals located in Thailand.

Method

Ethical approval for the study protocol had been approved by the Human Research Ethics Committee.

Subjects

Data for this retrospective chart review study were obtained from outpatient, inpatient and electronic medical records between January 1 and June 30, 2015. Eligible subjects for the study were newly diagnosed cancer patients receiving any intravenous CMT and were of age $\geq$ 18 years. Each CMT cycle in each treatment-naive patient initiating a new CMT course was included. We collected all CMT cycles during the study period and the following cycles until the planned CMT courses were completed. Patient demographic data, type of cancer, co-morbidity and MGFs prophylaxis was

recorded. FN risk assessment in each patient based on national comprehensive cancer network (NCCN) guideline; MGFs were evaluated for each cycle.

Prescribing patterns of MGFS

Prophylactic use of MGFs for FN was defined as primary prophylaxis in the first cycle of a CMT course, or where no neutropenic events occurred in the previous cycles. It was defined as secondary prophylaxis in the cycles after neutropenic events had occurred in the prior cycles.

In each cycle, for all patients, CMT regimen and risk of FN of CMT regimen were recorded. CMT regimens were classified to FN risk category as high (>20%), intermediate (10-20%) and low (<10%), based on the Guideline. Patient risk factors were composed of 1) older age (Age $\geq$ 65), 2) previous CMT or radiation therapy, 3) preexisting neutropenia or bone marrow involvement with tumor, 4) preexisting conditions (neutropenia, infection/open wounds, recent surgery), 5) poor performance status, 6) poor renal function, 7) liver dysfunction, most notably elevated bilirubin, and lastly, 8) HIV-infected patient (in particular, patients with low CD4 counts). We recorded "Yes" for patients with at least one existing risk factor, and recorded "No" for patients with no existing risk factors. In case of a "Yes" marking, the number of risk factors were also recorded.

According to the Guidelines (15-17), MGFs as primary prophylaxis are suggested if the overall FN risk is >20%. Therefore, MGFs prophylaxis is suggested for the use of CMT regimen with high and intermediate risk for FN with any additional patient risk factors. Prescribing MGFs in CMT cycles meeting the MGFs prophylaxis criteria from the Guideline was defined as 'used as recommended'. If there was no MGFs prophylaxis in the case needing such medications, we classified the cases as 'underuse'. Furthermore, the absence of MGFs prophylaxis in CMT cycles not meeting criteria for such prophylaxis was defined as 'not used' as recommended. If MGFs prophylaxis was given in the cases not meeting criteria for such prophylaxis, it was classified as 'overuse' group.

Outcome measurements

The outcomes of the study were CMT induced neutropenic events. FN was defined as a single temperature of $\geq$ 38.3°C taken orally, or $\geq$38.0°C over 1 hour plus neutropenia <500 neutrophils/mm^3, or <1,000 neutrophils/mm^3 with a predicted decline to $\leq$ 500/mm^3 over the next 48 hr. The severity levels of neutropenia were indexed from the Common Terminology Criteria for Adverse Events (CTCAE) (21) that classified severity using the ANC levels (Grade 1 to 4). Grades 3 neutropenia (ANC 1000 – 500/mm^3) and grade 4 neutropenia (ANC <500/mm^3) were defined as severe neutropenia. CMT dose delay was defined as a delay in planned CMT of 1 week or more, and CMT dose reduction was defined as a 15% or greater reduction in the planned dosage. We recorded the outcomes of CMT for every cycle.

Results

Patient characteristics

Data from 1,058 cycles of CMT were collected in 192 patients with 17 types of cancer. The average age of the patients was 56 years, with 47 patients being older than 65 years (24.48%). One-hundred and ten patients (57.29%) were female. The majority of cancer types were breast cancer (17.71%), head and neck cancer (15.63%), and cervical cancer (14.06%). The most common comorbid conditions were hypertension (21.88%), diabetes mellitus (13.02 %), and dyslipidemia (10.42%). The quantity of CMT regimen with high risk and intermediate risk for FN were 6.99% and 41.49%, respectively (Table 1).

MGFs usage

From the total of 1,058 CMT cycles, the pattern of MGFs usage consistent to the Guideline was 63.04%. In the view of primary prophylaxis, the pattern of MGFs usage consistent to the Guideline was 86.16%. On the contrast, the pattern of MGFs usage consistent to the Guideline was only 8.28% in secondary prophylaxis.

Table 1. Baseline characteristics of patients

characteristics	number (n =192)	percent
gender		
male	82	42.71
female	110	57.29
age (year): mean (56 ± 12 years)		
age > 65 years	47	24.48
co-morbidity[1]		
hypertension	42	21.88
diabetes mellitus	25	13.02
dyslipidemia	20	10.42
cardiovascular disease	8	4.17
benign prostatic hypertrophy	5	2.60
HIV/AIDS	4	2.08
gout	3	1.56
hyperthyroidism	3	1.56
hypothyroidism	2	1.04
thalassemia	1	0.52
epilepsy	1	0.52
chronic obstructive pulmonary disease	1	0.52
asthma	1	0.52
chronic hepatitis B	1	0.52
chronic hepatitis C	1	0.52

cancer type	patients (n =192)		CMT cycles (n =1,058)	
	number	percent	number	percent
breast cancer	34	17.71	257	24.29
head and neck cancer	30	15.63	136	12.85
cervical cancer	27	14.06	142	13.42
colorectal cancer	22	11.46	151	14.27
non-Hodgkin lymphoma	20	10.42	94	8.88
lung cancer	18	9.38	86	8.13
esophageal and gastric cancer	13	6.77	41	3.88
ovarian cancer	10	5.21	63	5.95
carcinoma of unknown primary	3	1.56	14	1.32
liver and bile duct cancer	3	1.56	12	1.13
bladder cancer	3	1.56	10	0.95
pancreatic cancer	2	1.04	7	0.66
thymoma cancer	2	1.04	14	1.32
endometrial cancer	2	1.04	10	0.95
skin cancer	1	0.52	10	0.95

Table 1. Baseline characteristics of patients (continued)

characteristics	number (n =192)		percent	
penile cancer	1	0.52	6	0.57
sarcoma	1	0.52	5	0.47
CMT FN risk (n =1,058)	number		percent	
primary prophylaxis (n=744)				
high	57		7.66	
intermediate	294		39.52	
low	393		52.82	
secondary prophylaxis (n=314)				
high	17		5.41	
intermediate	145		46.18	
low	152		48.41	

1: Some patients suffered from more than one underlying diseases

The most common pattern of secondary prophylaxis was underuse (91.72%). No CMT cycles in this study were classified as overuse (Table 2).

Four-hundred and sixty-seven cycles met the criteria for the MGFs prophylaxis, with 153 cycles as primary prophylaxis and 314 cycles as secondary prophylaxis. The consistency rate to the Guideline of MGFs use for primary and secondary prophylaxis was very different. For CMT with high FN risk, the consistency to the Guideline was at 63.16% for primary prophylaxis. In contrast, that in the intermediate FN risk CMT group was only 14.58%. In secondary prophylaxis, the results tended to be the same as that in primary prophylaxis. The consistency to the Guideline in high FN risk CMT, intermediate FN risk CMT and low FN risk CMT were 82.35%, 8.28%, and 0%, respectively (Figure 1).

CMT regimens with high-risk of FN were used in 4 types of cancer including head and neck cancer, sarcoma, non-Hodgkin lymphoma (NHL) and ovarian cancer. Within the primary prophylaxis group, all CMTs in head and neck cancer used MGFs prophylaxis, followed by the sarcoma cancer group, which used MGFs prophylaxis in 2 cycles out of the 3 cycles (‘used’ as recommended group; 66.67%), and then the NHL cancer group, which used MGFs prophylaxis in 62.00% of the cases. In the secondary prophylaxis group, MGFs prophylaxis was prescribed in both non-Hodgkin lympho

Table 2. Patterns of MGFs prophylaxis

patterns of MGFs	number of cycles (percent)		
	all (n=1,058)	primary prophylaxis (n = 744)	secondary prophylaxis (n = 314)
consistent to guideline	667 (63.04)	641 (86.16)	26 (8.28)
‘used’ as recommended	76 (7.18)	50 (6.72)	26 (8.28)
‘not used’ as recommended	591 (55.86)	591 (79.44)	0 (0.00)
inconsistent to guideline	391 (36.96)	103 (13.84)	288 (91.72)
underuse	391 (36.96)	103 (13.84)	288 (91.72)
overuse	0 (0.00)	0 (0.00)	0 (0.00)

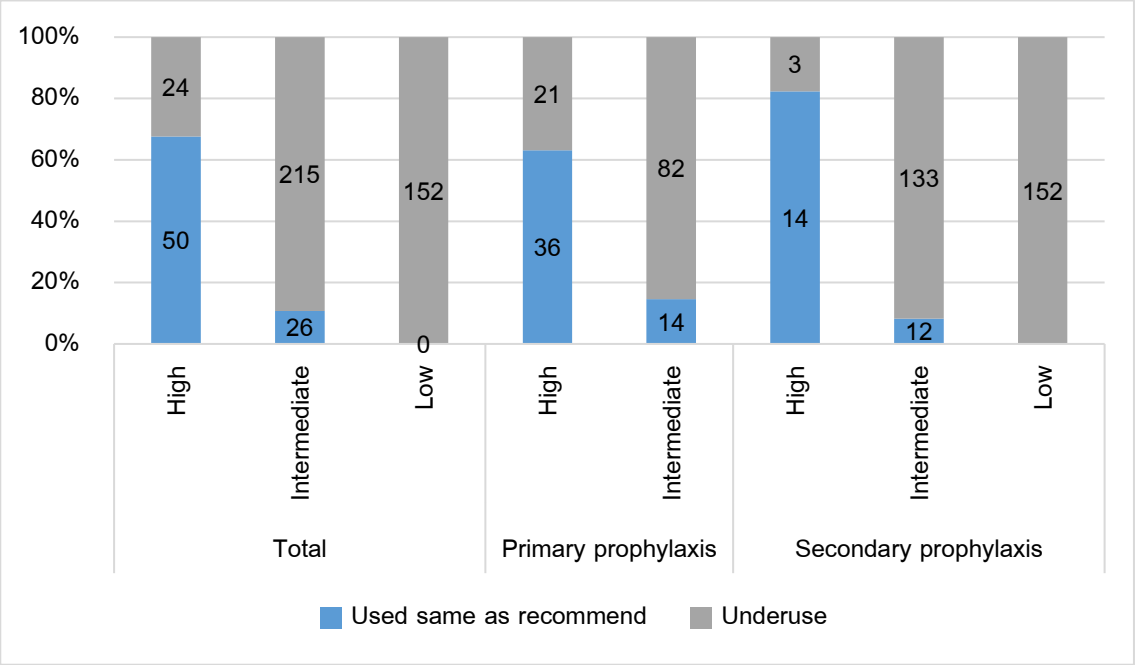

Figure 1. MGFs pattern of use in prophylaxis classified by FN risk chemotherapy

-ma and sarcoma. However, in all three cycles of ovarian cancer, MGFs prophylaxis was not used.

CMT regimens with intermediate risk for FN in patients with additional risk factors were used in 10 different types of cancer. Among primary prophylaxis, NHL was the most common cancer which MGFs prophylaxis was given consistent to the Guideline (71.43%), followed by breast cancer and thymoma. All CMT regimens classified as 'underuse' were in six types of cancer including bladder cancer, cervical cancer, colorectal cancer, endometrial cancer, lung cancer and ovarian cancer, followed by thymoma (70.00%). In secondary prophylaxis, MGFs prophylaxis was only used in NHL, with 100% of the CMT cycles receiving the MGFs prophylaxis. All CMT regimens were within the 'underuse' group in seven types of cancer including bladder cancer, breast cancer, cervical cancer, colorectal cancer, esophageal and gastric cancer, lung cancer, and ovarian cancer (Table 3)

MGFs was used as primary prophylaxis in 50 cycles and as secondary prophylaxis in 26 cycles. The mean durations of MGFs for primary prophylaxis and secondary prophylaxis were 6.8 ±1.19 days and 6.3 ±1.67 days, respectively. Among the cycles in which MGFs was used as primary prophylaxis and secondary prophylaxis, the most common usage was a 7-day regimen (80% and 57.69%, respectively). For all the cycles, drug and dose of MGFs prophylaxis was filgrastim 300 mcg/day. MGFs was used as primary prophylaxis most frequently in the CHOP regimen (60%), in patients with NHL, and as secondary prophylaxis most frequently in the R-CHOP regimen. NHL and sarcoma were the only two types of cancer in which MGFs was used as secondary prophylaxis (Table 4).

Neutropenia

Neutropenia occurred in 12 cancer types. All the occurrence was found in the 'underuse' group, except for the NHL and thymoma cancer types in which MGFs prophylaxis was prescribed. Severe neutropenia /delay CMT occurred in 14 cancer types which 4 cycles (5.26%) belonged to the 'used' as recommended group and 48 cycles (12.28%) in the 'underuse' group. FN (11.84%) occurred in spite of the administration of MGFs prophylaxis in the NHL and sarcoma groups. The occurrence of FN associated with other cancer types belonged to the 'underuse' group (Figure 2).

Table 3. Pattern of MGFs prophylaxis by cancer types

cancer type	primary prophylaxis		secondary prophylaxis	
	used as recommended	underuse	used as recommended	underuse
high FN risk chemotherapy (n = 74 cycles)				
head and neck cancer	3 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
non-Hodgkin lymphoma	31 (62.00)	19 (38.00)	12 (100.00)	0 (0.00)
ovarian cancer	0 (0.00)	1 (100.00)	0 (0.00)	3 (100.00)
sarcoma	2 (66.67)	1 (33.33)	2 (100.00)	0 (0.00)
intermediate FN risk chemotherapy (n = 241 cycles)				
bladder cancer	0 (0.00)	2 (100.00)	0 (0.00)	2 (100.00)
breast cancer	6 (35.29)	11 (64.71)	0 (0.00)	43 (100.00)
cervical cancer	0 (0.00)	1 (100.00)	0 (0.00)	5 (100.00)
colorectal cancer	0 (0.00)	32 (100.00)	0 (0.00)	42 (100.00)
endometrial cancer	0 (0.00)	10 (100.00)	0 (0.00)	0 (0.00)
esophageal and gastric cancer	0 (0.00)	0 (0.00)	0 (0.00)	4 (100.00)
lung cancer	0 (0.00)	13 (100.00)	0 (0.00)	10 (100.00)
non-Hodgkin lymphoma	5 (71.43)	2 (28.57)	12 (100.00)	0 (0.00)
ovarian cancer	0 (0.00)	4 (100.00)	0 (0.00)	27 (100.00)
thymoma	3 (30.00)	7 (70.00)	0 (0.00)	0 (0.00)

Discussion

Among the 1,058 CMT cycles in the study, 63.04% (667 cycles) of the use of MGFs prophylaxis were consistent with the Guideline. The main proportion was the 'not used' consistent to the recommendation (55.86%). The 'underuse' group (36.96%) was the majority of use inconsistent to the Guideline. No CMT cycles were classified as 'overuse'. However, the results from previous studies (16-18) found that some MGFs prophylaxis were overused.

Subgroup analysis to compare primary prophylaxis and secondary prophylaxis showed a drastic difference. For primary prophylaxis, 86.16% (641/744 cycles) of the MGFs prophylaxis were consistent to the Guideline. The majority of use was 'not used' consistent to the recommendation (79.44%). The other was 'used' as recommended in the Guideline (6.72%). Primary prophylaxis was used in 5 cancer types; breast cancer, non-Hodgkin lymphoma, sarcoma, thymoma and head and neck cancer. One-hundred and three CMT cycles (13.84%) belonged to the 'underuse' group inconsistent with the Guideline.

Three-hundred and fourteen CMT cycles were secondary prophylaxis. Among the secondary prophylaxis, only 8.28% (26 cycles) of the MGFs prophylaxis patterns were consistent with the Guideline. The number of CMT cycles inconsistent with the Guideline on MGFs prophylaxis were 288 cycles (91.72%) (classified as 'underuse' group). Only non-Hodgkin lymphoma and sarcoma cancer types received secondary prophylaxis. Other cancer types were classified as 'underuse'. Patterns of the 'underuse', 'overuse' and 'used' groups according to the recommendations in this study were consistent to those of previous studies (18-20).

The MGFs prophylaxis used in the CMT regimen with high risk of FN was accounted for 67.57% of the cycles (50 of 74 cycles), higher than that in

previous studies (18, 20). In the Ramsey et al. 's study (22), 50% of the high-risk patients received G-CSF, while in the Potosky et al. 's study (18), only 17% of the high-risk patients received prophylactic G-CSF. Among the high-risk group, non-Hodgkin lymphoma was the most common cancer type with MGFs prophylaxis.

Table 4. Usage patterns of primary and secondary prophylaxis

primary prophylaxis		chemotherapy cycles (n =50) number	percent
duration of MGFs (mean: 6.8 ±1.19 days)			
5 days		6	12.00
7 days		40	80.00
8 days		1	2.00
9 days		1	2.00
10 days		2	4.00
CMT regimen			
1. CHOP		30	60.00
2. TC		6	12.00
3. R-CHOP		5	10.00
4. cisplatin-docetaxel-5-fluorouracil		3	6.00
5. carboplatin-etoposide		3	6.00
6. doxifos		2	4.00
7. ESHAP		1	2.00
cancer type			
NHL	(CMT regimen 1,3,7)	36	72.00
breast cancer	(CMT regimen 2)	6	12.00
thymoma	(CMT regimen 5)	3	6.00
head and neck cancer	(CMT regimen 4)	3	6.00
sarcoma	(CMT regimen 6)	2	4.00
secondary prophylaxis		chemotherapy cycles (n =26) number	percent
duration of MGFs (mean: 6.3 ±1.67 days)			
5 days		9	34.62
7 days		15	57.69
10 days		2	7.69
CMT Regimen			
CHOP		8	30.77
ESHAP		2	7.69
doxifos		2	7.69
HyperCVAD		2	7.69
R-CHOP		12	46.15

Table 4. Usage patterns of primary and secondary prophylaxis (continued)

primary prophylaxis	chemotherapy cycles (n =50)	
	number	percent
cancer type		
non-Hodgkin lymphoma	24	92.31
CHOP	8	30.77
ESHAP	2	7.69
HyperCVAD	2	7.69
R-CHOP	12	46.15
sarcoma	2	7.69
doxifos	2	7.69

CMT Regimen with high risk 1. CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone 2. ESHAP = etoposide, methylprednisolone, cytarabine, cisplatin 3. cisplatin-oocetaxel-5-fluorouracil 4. doxifos=doxorubicin and ifosfamide 5. HyperCVAD = cyclophosphamide, vincristine, doxorubicin, dexamethasone

CMT Regimen with intermediate risk 1.TC = docetaxel, cyclophosphamide 2. R-CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab 3. carboplatin-etoposide

The rates of MGFs prophylaxis were 81.00%, 62.00% and 100.00% in Non-Hodgkin lymphoma group, primary prophylaxis group, and secondary prophylaxis group, respectively. These results parallel those in previous studies. The results from Link et al 's study (23) showed that G-CSF prophylaxis rate was 84.4% in malignant lymphoma patients, while the rate was about 13.4% in lung cancer. The rate of MGFs prophylaxis in sarcoma cancer was also high in this study, with 80.00% consistency with the Guideline. There was no MGFs

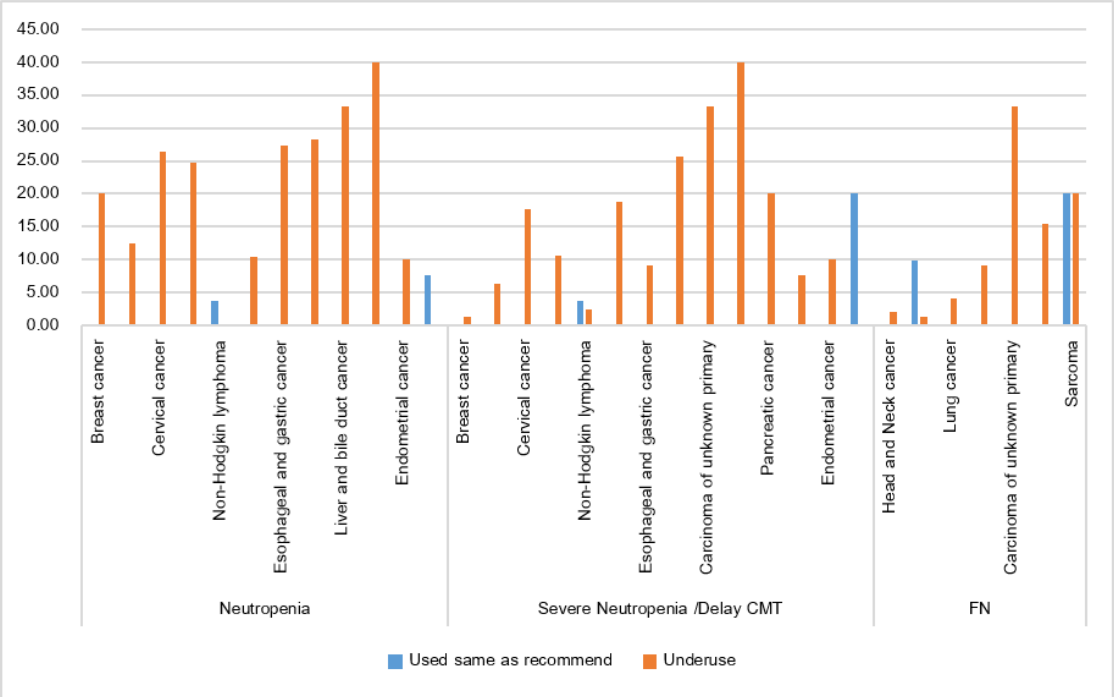

Figure 2. Comparison of abnormal clinical outcomes between 'used' according to the Guideline and the 'underuse' groups by cancer type

prophylaxis in ovarian cancer in any of the CMT cycles in this study, and were classified as the 'underuse' group. The rate of G-CSF prophylaxis in ovarian cancer in Krzemieniecki, et al 's study (24) was not high either. They were 20% and 19% for primary and secondary prophylaxis, respectively. Rate of MGFs prophylaxis in CMT regimens with intermediate risk for FN and any additional patient risk factors differed from that of CMT regimens with high risk. Majority of MGFs prophylaxis in this case was classified as 'underuse' (89.21%), especially those for secondary prophylaxis (91.72% or 133 of 145 cycles being classified as 'underuse'. The highest rate of MGFs prophylaxis was found in NHL (85.72%), with the similar rate as that in the CMT cases with high risk. In breast cancer, the rate was 35.29%. The rates found in the study were higher than that in Link et al's study (23). The rates in malignant lymphoma and breast cancer were 29.7% and 21.1%, respectively. Another study shows 55% and 21% of MGFs use for primary and secondary prophylaxis in breast cancer(25). The results in previous studies (25, 26) show 6.4%, 19% and 26% in MGFs prophylaxis for lung cancer. However, they were all classified as 'underuse' in this study.

MGFs primary prophylaxis was used in 7 types of CMT regimens and 5 types of cancer; NHL, breast cancer, thymoma, head and neck cancer and sarcoma. Most of the primary prophylaxis was prescribed in the CMT with high FN risk (36 cycles; 72%). CMTs with FN high risk in which the MGFs prophylaxis was prescribed were CHOP, ESHAP, cisplatin-docetaxel-5-FU and doxifos regimens. CMTs with intermediate risk (14 cycles; 28%) in which the MGFs prophylaxis was prescribed were the R-CHOP, TC and carboplatin-etoposide regimens in two NHL, one breast cancer and one thymoma patients, respectively. Other patients with same regimens did not receive MGFs prophylaxis. CMT patients with intermediate FN risk carried several risk factors. One patient in the NHL group was older (age 71 years) with stage 4 cancer, another had a poor renal function with 5 co-morbidities. One patient in the breast cancer group had bone metastasis with a higher FN rate compared to solid tumor (27). One patient in the thymoma group had metastasis, weight loss and liver dysfunction.

For secondary prophylaxis, MGFs were used in 26 cycles (8.28%), in 5 types of CMT regimens for 2 types of cancer. The regimen in 12 cycles (46.15%) was R-CHOP, which was classified as intermediate risk. More than half (53.85%) of the CMTs with high FN risk were composed of CHOP, ESHAP, HyperCVAD and doxifos regimens. Among the CMT regimens with intermediate risk, the majority of MGFs prophylaxis was classified as 'underuse'. The study by Link HL et al (23) was conducted to determine the reasons behind physicians' decision to prescribe MGFs prophylaxis. The reasons provided for the decision against the use of MGFs prophylaxis were no additional risk factors for FN, individual decision, low FN risks determined through personal experience, the use of G-CSF as secondary prophylaxis, the use of G-CSF only in cases where FN risk ≥40 %, institution's decision, and, in principle, no G-CSF. The most prominent reason was 'no additional risk factors for FN'. These findings in previous study may explain the absence of MGFs prophylaxis in the CMT regimens with intermediate risks in this study. Moreover, National List of Essential Medicine allowed secondary prophylaxis only in curative treatment thus this may affect the decision for prescribing prophylaxis even in the cases meeting the criteria in the Guideline. Further study is needed on the issue.

The longest duration of MGFs prophylaxis in this study was 7 days/CMT cycle (80% as primary prophylaxis, and 57.69% as secondary prophylaxis). The longest duration of MGFs prophylaxis used was 10 days, with 5 days duration used in 15 cycles. All MGFs prophylaxis used was filgrastim. The study by Weycker et al (28) showed that the risk of CMT-induced neutropenic complications was 2.4 and 1.9 times higher with 1–3 and 4–6 days of filgrastim prophylaxis, respectively, compared to that with ≥7 days. The mean duration of MGFs prophylaxis were 10-14 days in

clinical trials (28, 29). However, the duration is shorter in practice (30). Not only was the duration of MGFs prophylaxis concerned but also dose of filgrastim. Normally, the recommended dose for prophylaxis was 5 mcg/kg/dose. Lower dose resulted in a greater risk of FN, compared with the recommended one (31, 32). In this study, all patients received 300 mcg/day, the study did not determine how many patients received the drug with dose lower than the recommended one.

The MGFs prophylaxis was used as primary and secondary prophylaxis only in two cancer types; NHL and sarcoma. One sarcoma patient received 5 cycles of doxifos regimen in this stud with primary prophylaxis in the first two cycles. In the third cycle, no prophylaxis was provided and severe neutropenia (grade 4) occurred after CMT treatment. This patient received secondary prophylaxis in the rest of two cycles. The rate of neutropenia varied among cancer types, with the rate being higher in hematologic malignancies like leukemia and lymphoma, compared with solid tumors (27). A high FN rate (51%) in soft tissue sarcoma had been reported in the study by Aoyagi et al. (33). Therefore, there is a valid reason for MGFs prophylaxis in these two cancers. The patterns of MGFs prophylaxis in the study were similar to those in previous studies as mentioned above. The study was conducted in a tertiary care hospital and a teaching hospital as well. There were specialist physicians like oncologists, hematologists, radiologists, and also sub-board physicians such as a gynecologic oncologists and medical oncologists with intensive experiences in cancer treatment. Moreover, standard protocols for each CMT regimen and cancer type, which were created by specialist physicians, were used in this setting. The protocols were based on patient's demographic data such as weight, height, body surface area, CMT regimen and dose, pre-medication, starting date of CMT (day 1), follow-up date, as well as the results of the laboratory test on the follow up day. Hence, these protocols potentially improved the comprehensiveness of cancer patient care. In addition, the study by Wojtukiewicz et al (34) on the decision of physicians in prescribing MGFs prophylaxis in Poland showed that 75% of the questions were answered (correctly) in accordance to the Guidelines. The percentage of the correct answers was independent of the physicians' education level (specialization vs. lack of specialization), years of experience, type of health center, or geographic location (34).

This study was the first study to explore patterns of MGFs use to prevent CMT related FN. The strength of the study was the inclusion of all eligible patients which shown the patterns of MGFs prophylaxis in various type of cancer. There were also notable limitations in this study. First, the study was conducted in a single hospital, thus the result may not be generalizable to other settings with differences in CMT regimens, protocol and specialized physicians. Lastly, the retrospective design of the study can be associated with missing information and misclassification biases. The prospective study should be conducted to gain more definite answer.

Conclusions and suggestion

Primary MGFs prophylaxis used in the studied setting was more consistent with the Guideline than the secondary prophylaxis was. The prescription of MGFs prophylaxis in the high FN risk CMT group was high. On the other hand, MGFs prophylaxis in the intermediate FN risk CMT group was comparatively low. Non-Hodgkin lymphoma and sarcoma with a higher reported FN rate, were cancer types with the greatest adherence to the MGFs prophylaxis guideline. Most of the CMT regimens with MGFs prophylaxis were classified as high FN risk CMT. The rate of MGFs prophylaxis, both in the CMT regimen with high and intermediate risks and any additional patient risk factors varied among various cancer types. The results are expected to indicate as well as enhance the awareness

of MGFs prophylaxis usage in the clinical practice especially in the intermediate FN risk CMT group.

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References

1. Kobayashi SD, DeLeo FR. Role of neutrophils in innate immunity: a systems biology-level approach. Wiley Interdiscip Rev Syst Biol Med. 2009; 1: 309-33.
2. Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. Cancer. 2005;103:1916-24.
3. 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.
4. Weycker D, Barron R, Kartashov A, Legg J, Lyman GH. Incidence, treatment, and consequences of chemotherapy-induced febrile neutropenia in the inpatient and outpatient settings. J Oncol Pharm Pract. 2014;20:190-8.
5. Chindaprasirt J, Wanitpongpun C, Limpawattana P, Thepsuthammarat K, Sripakdee W, Sookprasert A, et al. Mortality, length of stay, and cost associated with hospitalized adult cancer patients with febrile neutropenia. Asian Pac J Cancer Prev. 2013;14:1115-9.
6. Lyman GH, Dale DC. Hematopoietic growth factors in oncology. In: Rosen ST, editor: Cancer treatment and research: Springer; 2011. p.109-66.
7. Vogel CL, Wojtukiewicz MZ, Carroll RR, Tjulandin SA, Barajas-Figueroa LJ, Wiens BL, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. J Clin Oncol. 2005;23:1178-84.
8. Bohlius J, Herbst C, Reiser M, Schwarzer G, Engert A. Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. Cochrane Database Syst Rev. 2008(4) :Cd003189.
9. Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J. Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. Ann Intern Med. 2007; 147: 400-11.
10. Wang L, Baser O, Kutikova L, Page JH, Barron R. The impact of primary prophylaxis with granulocyte colony-stimulating factors on febrile neutropenia during chemotherapy: a systematic review and meta-analysis of randomized controlled trials. Support Care Cancer. 2015;23:3131-40.
11. Lee S, Knox A, Zeng IS, Coomarasamy C, Blacklock H, Issa S. Primary prophylaxis with granulocyte colony-stimulating factor (GCSF) reduces the incidence of febrile neutropenia in patients with non-Hodgkin lymphoma (NHL) receiving CHOP chemotherapy treatment without adversely affecting their quality of life: cost-benefit and quality of life analysis. Support Care Cancer. 2013;21:841-6.
12. Aarts MJ, Grutters JP, Peters FP, Mandigers CM, Dercksen MW, Stouthard JM, et al. Cost effectiveness of primary pegfilgrastim prophylaxis in patients with breast cancer at risk of febrile neutropenia. J Clin Oncol. 2013;31:4283-9.
13. Hirsch BR, Lyman GH. Pharmacoeconomics of the myeloid growth factors: a critical and systematic review. Pharmacoeconomics. 2012;30:497-511.
14. Barnes G, Pathak A, Schwartzberg L. Pharmaco economics of granulocyte colony-stimulating factor: a critical review. Adv Ther. 2014;31:683-95.
15. National Comprehensive Cancer Network. NCCN Clinical practice guidelines in oncology, myeloid growth factors [online]. 2015 [cited on Oct 26,

2015]. Available from: www.nccn.org/professionals/ physician_gls/pdf/myeloid_growth.pdf.

16. 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.
17. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011;47:8-32.
18. Potosky AL, Malin JL, Kim B, Chrischilles EA, Makgoeng SB, Howlader N, et al. Use of colony-stimulating factors with chemotherapy: opportunities for cost savings and improved outcomes. J Natl Cancer Inst. 2011; 103: 979-82.
19. Waters GE, Corrigan P, Gatesman M, Smith TJ. Comparison of pegfilgrastim prescribing practice to national guidelines at a university hospital outpatient oncology clinic. J Oncol Pract. 2013;9:203-6.
20. Barnes G, Pathak A, Schwartzberg L. G-CSF utilization rate and prescribing patterns in United States: associations between physician and patient factors and GCSF use. Cancer Med. 2014;3:1477-84.
21. National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. [online]. 2010 [cited on Oct 26, 2015]. Available from: evs.nci.nih. gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_Quick Reference_5x7.pdf.
22. McCune JS, Sullivan SD, Blough DK, Clarke L, McDermott C, Malin J, et al. Colony-stimulating factor use and impact on febrile neutropenia among patients with newly diagnosed breast, colorectal, or non-small cell lung cancer who were receiving chemotherapy. Pharmacotherapy. 2012;32:7-19.
23. Link H, Nietsch J, Kerkmann M, Ortner P. Adherence to granulocyte-colony stimulating factor (G-CSF) guidelines to reduce the incidence of febrile neutropenia after chemotherapy--a representative sample survey in Germany. Support Care Cancer. 2016; 24: 367-76.
24. Krzemieniecki K, Sevelda P, Erdkamp F, Smakal M, Schwenkglenks M, Puertas J, et al. Neutropenia management and granulocyte colony-stimulating factor use in patients with solid tumours receiving myelotoxic chemotherapy--findings from clinical practice. Support Care Cancer. 2014;22:667-77.
25. Lyman GH, Kleiner JM. Summary and comparison of myeloid growth factor guidelines in patients receiving cancer chemotherapy. Cancer Treat Res. 2011;157:145-65.
26. McCall K, Johnston B. Treatment options in end-of-life care: the role of palliative chemotherapy. Int J Palliat Nurs. 2007;13:486-8.
27. 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.
28. Weycker D, Barron R, Edelsberg J, Kartashov A, Legg J, Glass AG. Risk and consequences of chemotherapy-induced neutropenic complications in patients receiving daily filgrastim: the importance of duration of prophylaxis. BMC Health Serv Res. 2014;14:189.
29. Lin WT, Wen YW, Chien CR, Gau CS, Chiang SC, Hsiao FY. Suboptimal duration of granulocyte colony-stimulating factor use and chemotherapy-induced neutropenia in women diagnosed with breast cancer. Clin Ther. 2014;36:1287-94.
30. Mitchell S, Li X, Woods M, Garcia J, Hebard-Massey K, Barron R, et al. Comparative effectiveness of granulocyte colony-stimulating factors to prevent febrile neutropenia and related complications in cancer patients in clinical practice: A systematic review. J Oncol Pharm Pract. 2016;22:702-16.

31. Ip EJ, Lee-Ma A, Troxell LS, Chan J. Low-dose filgrastim in patients with breast cancer treated with docetaxel, doxorubicin, and cyclophosphamide. Am J Health Syst Pharm. 2008;65:1552-5.
32. J KH, D KO, Broyles JE, S CW. Impact of recom mended weight-based dosing of granulocyte-colony stimulating factors in acute leukemia and stem cell transplant patients. Support Care Cancer. 2017; 25: 1853-8.
33. Aoyagi T, Morii T, Tajima T, Yoshiyama A, Ichimura S. Analysis of the risk factors for febrile neutropenia in patients with bone and soft tissue sarcoma. Anticancer Res. 2015;35:2375-83.
34. Wojtukiewicz M, Chmielowska E, Filipczyk-Cisarz E, Krzemieniecki K, Lesniewski-Kmak K, Litwiniuk MM, et al. Clinical practice in febrile neutropenia risk assessment and granulocyte colony-stimulating factor primary prophylaxis of febrile neutropenia in Poland. Contemp Oncol (Pozn). 2014;18:419-24.