Original Article

Efficacy of granulocyte colony stimulating factor as a secondary prophylaxis along with full-dose chemotherapy following a prior cycle of febrile neutropenia

Seema Gupta[1,*], Pankaj K. Singh[1], Madan L. B. Bhatt[1], Mohan C. Pant[1], Rajeev Gupta[1], Mahendra P. S. Negi[2]

[1] *Department of Radiotherapy, C.S.M. Medical University, Lucknow, India;*
[2] *Biometry and Statistics Division, Central Drug Research Institute, Lucknow, India.*

Summary **Secondary prophylaxis with recombinant human granulocyte colony stimulating factor (G-CSF) is recommended where patients have experienced febrile neutropenia in an earlier chemotherapy cycle and for whom the maintenance of chemotherapy dose intensity is important; or where febrile neutropenia has not occurred but prolonged neutropenia is causing excessive dose delay or reduction, where maintenance of dose intensity is important. The objective of this study was to determine the efficacy and feasibility of G-CSF as secondary prophylaxis when used along with full dose moderately myelotoxic chemotherapy following a prior cycle with febrile-neutropenia. Fifty-two patients aged 22-75 years with febrile neutropenia that required intravenous antibiotics following moderately myelotoxic chemotherapy were included. These patients received the next cycle of the same chemotherapy regime without dose modification but with support of filgrastim 24 h after completion of chemotherapy (300 µg/day/subcutaneously (*s.c.*) for weight < 60 kg, 480 µg/day/*s.c.* for weight > 60 kg, for at least 10 consecutive days), patients in whom neutropenia was associated with a life-threatening infection and those who developed prolonged myelosuppression were excluded. The use of the hematopoietic growth factor G-CSF was shown to shorten the neutrophil recovery time, resulting in significant reduction of incidence of febrile neutropenia, hospitalization and use of broad spectrum antibiotics. There was no drug related death or adverse events associated with either cycle. In conclusion, recombinant human G-CSF is effective and relatively safe as a secondary prophylaxis with full dose chemotherapy in patients who develop febrile neutropenia following prior cycles of moderately myelotoxic chemotherapy.**

Keywords: Febrile neutropenia, G-CSF, toxicity, chemotherapy, antibiotics

1. Introduction

Association of neutropenia and infection continues to be a major cause of morbidity and mortality in cancer patients receiving myelosuppressive chemotherapy (*1*). Prompt initiation of empiric broad-spectrum antibiotics has effectively improved the outcome of patients with febrile neutropenia. However, a substantial proportion of these patients require prolonged hospital stays or develop more severe medical complications.

Febrile neutropenia is defined as an absolute neutrophil count (ANC) of $< 0.5 \times 10^9$/L and an oral temperature of > 38°C and is a serious consequence of chemotherapy-induced neutropenia (CIN), frequently resulting in hospitalization, infectious complications, the use of intravenous (*i.v.*) antibiotics, chemotherapy dose delays or reductions, reduced treatment effectiveness, increased health care expenditures, reduced quality of life, and possibly death (*2-9*).

Hematopoietic colony-stimulating factor (CSF), such as granulocyte CSF (G-CSF) has shown to promote proliferation, differentiation, and function of

*Address correspondence to:
Dr. Seema Gupta, Department of Radiotherapy, C.S.M. Medical University, Lucknow, Uttar Pradesh 226003, India.
e-mail: seemagupta02@sify.com

progenitor and mature cells of the myeloid lineage (*10*). These cytokines also stimulate the bactericidal functions of mature neutrophils (*11*). When administered as a preventive adjunct to chemotherapy, CSFs have shown in clinical trials to shorten the neutropenic period and to reduce by 50% the incidence of febrile neutropenia in high-risk patients (*3,7,12*).

A recent meta-analysis of randomized controlled trials evaluating the treatment of febrile neutropenia with G-CSFs plus antibacterials *vs.* antibacterials alone demonstrated a significant reduction in the proportion of patients with prolonged hospitalization among those who received G-CSFs (*13,14*). The occurrence of neutropenia can lead to a delay in subsequent cycles of chemotherapy or a reduction in the doses of drugs in the regimen, which can compromise the efficacy of the chemotherapy (*4,5*). In aggressive non-Hodgkin's lymphoma (NHL) and early-stage breast cancer, there are data suggesting that the administration of a chemotherapy planned dose on time is associated with improved outcomes (*5-9,15-18*).

Several recent studies have shown that many patients, particularly older individuals, are routinely given both lower planned and delivered chemotherapy doses than the standard reference regimens (*15-18*). However, clinical trial data show that older patients can have outcomes (overall survival and disease free survival) similar to those of younger patients when adequate (*i.e.*, literature-cited, standard-dose) chemotherapy dose intensity is delivered (*19-21*). Furthermore, it has been suggested that older patients are more susceptible to myelotoxicity, possibly because of decreased hematopoietic reserves (*22,23*). The National Comprehensive Cancer Network (NCCN), USA, recently published guidelines recommending that patients aged 70 years and over who are treated with moderately toxic regimens should be treated prophylactically with hematopoietic growth factors (HGFs) to reduce myelotoxicity of the chemotherapy planned dose on time (*23*). Therefore CIN is clearly a serious consequence of myelosuppressive chemotherapy, but it can be managed successfully.

The optimal strategy is to prevent occurrence of neutropenia, and in patients with an increased risk of developing chemotherapy-related infections, prophylactic administration of CSFs may be warranted (*3*). Published data clearly establish that the optimal use of filgrastim requires initiation 24 to 72 h after the completion of the chemotherapy (*3*) and that delaying the start of filgrastim until the time of the ANC nadir is less effective. Furthermore, the administration of G-CSF over all cycles of chemotherapy leads to a cumulative benefit in terms of reduced incidence and duration of severe neutropenia in later cycles compared with cycle 1. This is thought to be due to a priming effect of G-CSF on neutrophil recovery by enhancing cell differentiation of the post-mitotic pool (*7*).

This study aimed to evaluate the efficacy and feasibility of G-CSF as a secondary prophylaxis when used along with full dose moderately myelotoxic chemotherapy following a prior cycle with febrile-neutropenia in solid tumors.

2. Materials and Methods

2.1. *Patients*

Between January 2003 and December 2008, 52 patients with febrile neutropenia that required intravenous antibiotics following moderately myelotoxic chemotherapy were included. The age of patients was in a range of 22-75 years (median 47). These patients received the next cycle of the same chemotherapy regime without dose modification but with support of filgrastim (300 μg/day/*s.c.* for weight < 60 kg, 480 μg/day/*s.c.* for weight > 60 kg, for at least 10 consecutive days) if the following criteria were fulfilled: age 18-70 years, WHO performance status ≤ 2, febrile neutropenia during last cycle not associated with septicemia or other life-threatening infection; complete recovery of neutrophils (> 1,500/mm^3) and platelets (> 100,000/mm^3) on the first day of the following cycle and the last chemotherapy cycle not associated with dose-limiting toxicity other than febrile neutropenia. Patients in whom neutropenia was associated with a life-threatening infection and those who developed prolonged myelosuppression were excluded. Diagnoses included lymphoma (*n* = 22), breast cancer (*n* = 21), germ cell tumor (*n* = 3), or non-small cell lung cancer (*n* = 6). Filgrastim (300 mg/day) was given subcutaneously starting 24-30 h after the last chemotherapy dose. A total of 8-9 alternate day doses were given routinely. However, if the absolute neutrophil count did not reach 1,500/mm^3 after the neutrophil nadir, G-CSF was given for a longer period. Subsequent cycles were given with filgrastim support and without dose reductions if no other dose limiting toxicity developed. Data concerning the incidence of febrile neutropenia, infection, and other dose-limiting toxicities that developed during the first four cycles given with secondary G-CSF prophylaxis were analyzed.

All patients signed a standard informed consent form before the start of each chemotherapy regimen.

2.2. *Study end points*

Primary end point was the duration of hospital stay. Secondary end points were, days on antibiotic therapy, incidence of fever, time to resolve fever, dose reduction, dose delay, and any incidence of adverse events in successive cycles of chemotherapy.

2.3. *Statistical analysis*

Groups (cycles) were compared using non parametric Friedman one way analysis of variance (ANOVA) by ranks followed by Dunn's multiple comparison test. Rank correlation was used to calculate relative association among the measures (variables). Proportions were compared by χ^2 and proportion Z-test. A two-tailed ($\alpha = 2$), probability (p) value less than 0.05 ($p < 0.05$) was considered to be statistically significant. MS EXCEL (MS Office 97-2003) and GraphPad Prism (version 5) were used for the analysis.

Table 1. Characteristics of patients (*n* = 52) treated with prophylactic G-CSF

Characteristics/Diagnosis/Treatment	Number of Patients
Characteristics	
Median age in yrs (range)	47 (22-75)
Diagnosis	
Lymphoma number (%)	22 (42.31%)
Breast cancer number (%)	21 (40.38%)
Testicular germ cell tumor number (%)	3 (5.77%)
Non small cell lung cancer number (%)	6 (11.54%)
Treatment	
CHOP/CHOP like number	18
COPP	2
ABVD	2
PEB	3
Cisp/Etop	6

3. Results

3.1. *Patients and chemotherapy regimens*

Fifty-two consecutive patients who fulfilled the study criteria were treated between January 2003 and December 2008. The major characteristics, diagnosis and their treatment regimens associated with neutropenic fever are shown in Table 1. As can be seen, the most common diagnosis was lymphoma (42%) and breast cancer (40%). More than half (58%) received adriamycin-containing regimens. Chemotherapy was given as adjuvant or neoadjuvant therapy.

Two patients in whom neutropenia was associated with a life-threatening infection and those who developed prolonged myelosuppression during the treatment were excluded from the study. Thus, efficacy of prophylactic G-CSF was investigated on 50 patients and evaluated statistically.

3.2. *End measures*

The end measures such as neutrophil recovery time, duration of fever, duration of antibiotic and duration of hospitalization are summarized graphically in Figure 1. Figure 1 showed that all these measures decrease with the progression of cycles. Inter comparison of

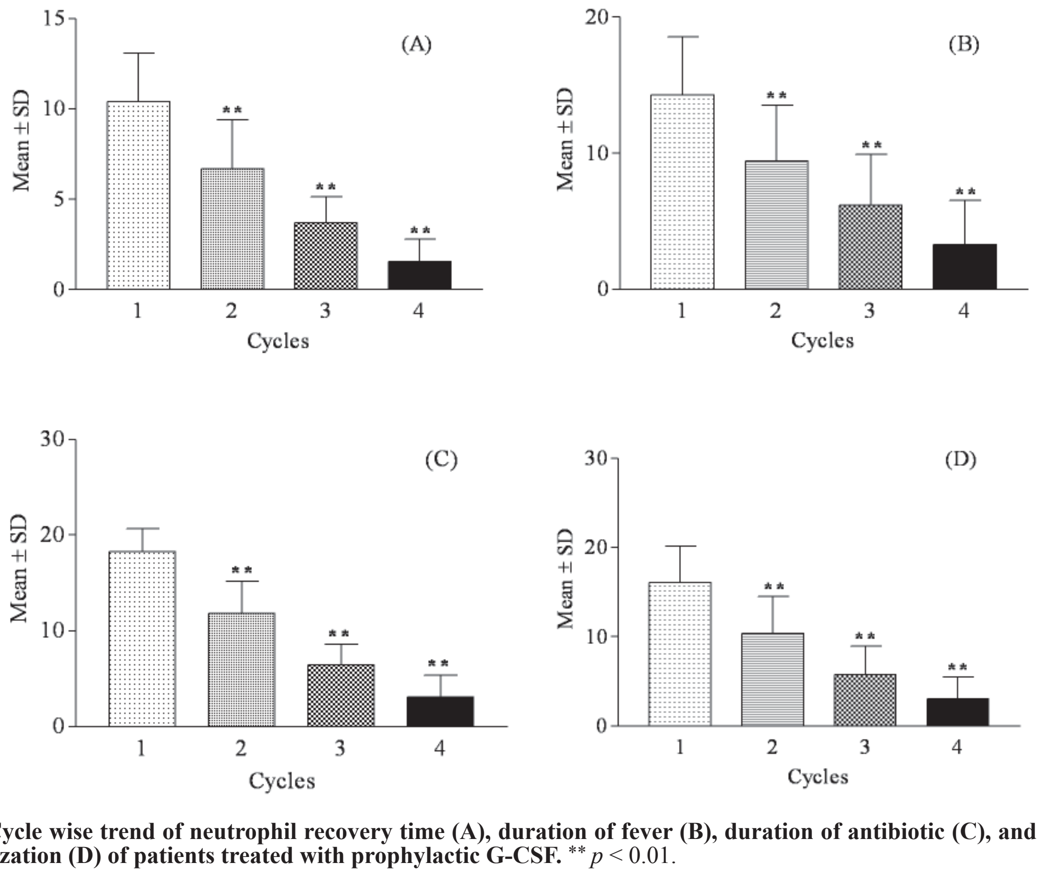

Figure 1. Cycle wise trend of neutrophil recovery time (A), duration of fever (B), duration of antibiotic (C), and duration of hospitalization (D) of patients treated with prophylactic G-CSF. ** $p < 0.01$.

Table 2. End measures at 4 cycles of patients (n = 50) treated with prophylactic G-CSF

Measures	Cycles 1	2	3	4	χ^2 (DF = 12)
Incidence of febrile neutropenia	32	9	5	2	
Incidence of antibiotic	32	9	5	2	
Incidence of antifungal	6	1	0	0	4.37^{ns}
Cycle delay	12	4	1	0	
Dose reduction	13	6	2	0	

Data represents number of patients. $^{ns}p > 0.05$.

Table 3. Inter-correlation (n = 200) among variables

Variables	Cycles	Neutrophil recovery time	Duration of fever	Duration of antibiotic	Duration of hospitalization	Incidence of fever	Incidence of antibiotic	Incidence of antifungal	Cycle delay	Dose reduction
Cycles	1.00									
Neutrophil recovery time	−0.90*	1.00								
Duration of fever	−0.52*	0.58*	1.00							
Duration of antibiotic	−0.53*	0.57*	0.97*	1.00						
Duration of hospitalization	−0.53*	0.57*	0.97*	1.00*	1.00					
Incidence of fever	−0.49*	0.56*	0.97*	0.92*	0.92*	1.00				
Incidence of antibiotic	−0.49*	0.52*	0.95*	0.99*	0.99*	0.92*	1.00			
Incidence of antifungal	−0.23*	0.24*	0.25*	0.26*	0.25*	0.21*	0.21*	1.00		
Cycle delay	−0.31*	0.35*	0.43*	0.44*	0.44*	0.37*	0.37*	0.43*	1.00	
Dose reduction	−0.31*	0.34*	0.56*	0.54*	0.54*	0.53*	0.49*	0.29*	0.60*	1.00

* $p < 0.01$

groups (cycle) showed the median (or mean) values of all these measures decreased significantly ($p < 0.01$) in cycle 2, 3, and 4 as compared to cycle 1 (Figure 1) while the levels of all these did not differ significantly ($p > 0.05$) in cycle 2, 3, and 4 except neutrophil recovery time. The neutrophil recovery time in cycle 3 and 4 also decreased significantly ($p < 0.05$) from cycle 2, while the level in cycle 3 and 4 did not differ significantly ($p > 0.05$) *i.e.*, were found to be statistically the same.

The other end measures such as incidence of fever, antibiotic, antifungal, cycle delay and dose reduction in patients are summarized in Table 2. Table 2 showed that as cycles increased the incidence of these measures in patients decreased. When compared the decrease in all measures over the cycles were found to be insignificant ($\chi^2 = 4.37$, $p > 0.05$).

The inter-correlation of all the above end measures over cycles (1 to 4) is summarized in Table 3. All measures showed a significant ($p < 0.01$) and inverse (negative value) correlation with the progression of cycles *i.e.*, as number of cycles increases, the incidence of symptoms decreases while the correlation among measures were found to be positive and significant ($p < 0.01$).

The initial and final evaluations of adverse events in patients are summarized in Table 4. All adverse events in patients decreased significantly ($p < 0.05$ or $p < 0.01$) in the final evaluation as compared to the initial except, diarrhea, musculoskeletal pain (severe, moderate, mild), and Grade III mucositis/stomatitis.

Table 4. Adverse events in patients (n = 50) treated with prophylactic G-CSF

Adverse events	Initial (n)	Final (n)	Z-test
Vomiting grade III	15	3	2.86**
Fatigue	13	2	2.80**
Diarrhea	7	3	1.00^{ns}
Anemia	10	1	2.56*
Fever	32	2	6.12**
Musculoskeletal pain	19	Same	No change
Severe	6	Same	No change
Moderate	6	Same	No change
Mild	7	Same	No change
Weakness	30	2	5.79**
Dizziness	20	1	4.42**
Grade III mucositis/stomatitis	7	1	1.84^{ns}

$^{ns}p > 0.05$; $^{*}p < 0.05$; $^{**}p < 0.01$.

4. Discussion

The American society of clinical oncology (ASCO-2005) and ASCO-2005 update guidelines support the use of secondary prophylactic G-CSF in patients who had experienced a neutropenic complication (febrile neutropenia or prolonged neutropenia) from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease free or overall survival or treatment outcome. The ASCO-2005 update gives evidence that G-CSF recipients experienced fewer episodes of hospitalization for febrile neutropenia and greater dose-intensity compared to historical controls *i.e.*, CSF support, but none of the other significant clinical outcomes (survival, quality of life, toxicity or cost) were reported (*1*).

Several relevant studies have been reported since 2000. In a multicenter trial conducted in Spain, adult patients with solid tumors or lymphoma who developed febrile neutropenia and had at least one high-risk factor, were treated with intravenous antibiotics and randomly assigned to receive G-CSF (5 µg/kg per day) until neutrophil recovery. CSF recipients had a shorter period of grade 4 neutropenia (median 2 *vs.* 3 days, $p = 0.0004$), antibiotic therapy (median 5 *vs.* 6 days, $p = 0.013$), and hospital stay (median 5 *vs.* 7 days, $p = 0.015$) (*2*). Survival between groups was similar.

In a Cochrane systematic review and meta-analysis, which included 1,518 patients from 13 trials, patients randomized to receive CSF experienced less prolonged neutropenia [25% *vs.* 45%; OR = 0.32 (0.23-0.46); $p <$ 0.00001], less prolonged hospitalization [23% *vs.* 32%; OR = 0.63 (0.49-0.82); $p = 0.0006$], marginally less infection related mortality [3.1% *vs.* 5.7%; OR = 0.51 (0.26-1.00); $p = 0.05$] and no significant difference in overall mortality [5.1% *vs.* 7.1%; OR = 0.68 (0.43-1.06); $p = 0.10$] (*2*). Bone, joint pain, and arthralgias were more common in CSF treated patients ($p = 0.007$).

Studies have reported that hypotension and bacteremia in the setting of neutropenia are significant risk factors for prolonged hospitalization (> 7 days) and high mortality. Malik *et al.* reported that mortality rate is associated with febrile neutropenia in patients presenting with shock of 82% (*3*). A study from France reported that patients admitted to an ICU with febrile neutropenia experienced a 54% 30-day mortality rate (*4*).

The chemotherapy regimens used in the current study were moderately myelotoxic. Patients treated with highly myelotoxic regimens received primary G-CSF prophylaxis and were not included in this study.

During the study period, our departmental policy of full-dose administration with secondary G-CSF support was limited to patients with solid tumors who were being treated with an intention for cure or for durable remission. This explains the relatively high proportion of patients with lymphoma (42%) and breast cancer (40%). It is noteworthy that a substantial portion of patients with potentially curable histologically aggressive non-Hodgkin's lymphoma (*5*) and breast cancer patients treated with adjuvant chemotherapy (*6*) have reductions and/or delays in dosage, mostly due to neutropenia. Therefore, secondary G-CSF prophylaxis may play an important role in sustaining dose-intensity in patients with these diagnoses.

Controlled trials show beneficial effects of filgrastim on hospitalization, antibiotic use, incidence of neutropenia with fever, and chemotherapy dosing compared with placebo, when started 24 h after the last dose of chemotherapy (*7-9,15*). Delaying the start of filgrastim therapy beyond 72 h has suboptimal effects on hematological recovery and infection-related endpoints (*16,17*). The use of filgrastim following consecutive cycles of chemotherapy appears to confer cumulative benefits in the management of neutropenia associated complications (*7*).

Our data also demonstrate that, following conventional chemotherapy associated with uncomplicated neutropenic fever, the same regimen can be safely given without dose reduction with secondary G-CSF prophylaxis, given 24 h after the last dose of chemotherapy. The incidence of febrile neutropenia during the first cycle of chemotherapy given with filgrastim supported 32/50 (64%) patients which gradually was reduced to 9/50 (18%) in the second cycle, 5/50 (10%) in the third cycle, and 2/50 (4%) in the fourth cycle. Furthermore, there was no evidence of bacterial infection or other serious infection in any of these patients. Importantly, the rate of other dose-limiting toxicities in patients treated with full dose chemotherapy with filgrastim support was very low and included grade 3 mucositis that developed in one patient in the fourth cycle of chemotherapy with G-CSF.

5. Conclusion

G-CSF secondary prophylaxis may be justified in patients who have experienced a previous febrile episode or prolonged neutropenia, for whom the maintenance of dose intensity is important, *e.g.* those with primary breast cancer, advanced hodgkins disease, or intermediate/high-grade non-Hodgkin's lymphoma (NHL). G-CSF should be started 24-hour post chemotherapy at a dose of 5 µg/kg/day. If delayed for more than 72 h, benefits may be lost. G-CSF administration should be continued until the expected nadir has passed and the neutrophil count has recovered into the normal range. Filgrastim administration through repeated cycles of chemotherapy appears to confer cumulative benefits. Our data also show that a policy of full-dose administration of moderately myelotoxic chemotherapy with G-CSF following a prior cycle that was associated with uncomplicated febrile neutropenia is feasible and relatively safe. Thus, we can say that secondary G-CSF prophylaxis may play an important role in sustaining dose-intensity in these patients.

Thus it is now established that the use of G-CSF will significantly reduce the degree and duration of chemotherapy-induced neutropenia with a substantial reduction in infection and associated morbidity. It was also expected that such a rapid recovery of neutrophils would allow chemotherapy to be given on time and at the appropriate dose. This would be accompanied by an improved tumor response. This goal has not been realized but awaits further adequately-sized randomized studies.

Acknowledgements

Authors are thankful to the Director of CDRI, Lucknow (India), for his encouragement and support.

References

1. Smith TJ, Khatcheressian J, Lyman GH, *et al.* 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol. 2006; 24:3187-3205.
2. Clark OA, Lyman GH, Castro AA, Clark LG, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia: A meta-analysis of randomized controlled trials. J Clin Oncol. 2005; 23:4198-4214.
3. Malik I, Hussain M, Yousuf H. Clinical characteristics and therapeutic outcome of patients with febrile neutropenia who present in shock: Need for better strategies. J Infect. 2002; 42:120-125.
4. Darmon M, Azoulay E, Alberti C, Fieux F, Moreau D, Le Gall JR, Schlemmer B. Impact of neutropenia duration on short-term mortality in neutropenic critically ill cancer patients. Intensive Care Med. 2002; 28:1775-1780.
5. Lyman GH, Dale DC, Friedberg J, Crawford J, Fisher RI. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-hodgkin's lymphoma: A nationwide study. J Clin Oncol. 2004; 22:4302-4311.
6. Frasci G. Treatment of breast cancer with chemotherapy in combination with filgrastim: Approaches to improving therapeutic outcome. Drugs. 2002; 62 (Suppl):17-31.
7. Crawford J, Ozer H, Stoller R, *et al.* Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med. 1991; 325:164-170.
8. Trillet-Lenoir V, Green J, Manegold C, Von Pawel J, Gatzemeier U, Lebeau B, Depierre A, Johnson P, Decoster G, Tomita D, Ewen C. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. Eur J Cancer. 1993; 29:319-324.
9. de Graaf H, Willemse PH, Bong SB, Piersma H, Tjabbes T, van Veelen H, Coenen JL, de Vries EG. Dose intensity of standard adjuvant CMF with granulocyte colony-stimulating factor for premenopausal patients with node-positive breast cancer. Oncology. 1996; 53:289-294.
10. Souza LM, Boone TC, Gabrilove J, Lai PH, Zsebo KM, Murdock DC, Chazin VR, Bruszewski J, Lu H, Chen KK, Barendt J, Platzer E, Moore MA, Mertelsmann R, Welte K. Recombinant human granulocyte colony-stimulating factor: Effects on normal and leukemic myeloid cells. Science. 1986; 232:61-65.
11. Metcalf D. The colony stimulating factors. Discovery, development, and clinical applications. Cancer. 1990; 65:2185-2195.
12. García-Carbonero R, Mayordomo JI, Tornamira MV, *et al.* Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: A multicenter randomized trial. J Natl Cancer Inst. 2001; 93:31-38.
13. Clark OA, Lyman G, Castro AA, Clark LG, Djulbegovic B. Colony stimulating factors for chemotherapy induced febrile neutropenia. Cochrane Database Syst Rev. 2000; (3):CD003039.
14. Clark OA, Lyman GH, Castro AA, Clark LG, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia: A meta-analysis of randomized controlled trials. J Clin Oncol. 2005; 23:4198-4214.
15. Heil G, Hoelzer D, Sanz MA, Lechner K, Liu Yin JA, Papa G, Noens L, Szer J, Ganser A, O'Brien C, Matcham J, Barge A. A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with *de novo* acute myeloid leukemia. The International Acute Myeloid Leukemia Study Group. Blood. 1997; 90:4710-4718.
16. Crawford J, Kreisman H, Garewal H, Jones SE, Shoemaker D, Pupa MR, Armstrong S, Tomita D, Dziem G. The impact of Filgrastim schedule variation on hematopoietic recovery post-chemotherapy. Ann Oncol. 1997; 8:1117-1124.
17. Koumakis G, Vassilomanolakis M, Barbounis V, Hatzichristou E, Demiri S, Plataniotis G, Pamouktsoglou F, Efremidis AP. Optimal timing (Preemptive *versus* supportive) of granulocyte colony-stimulating factor administration following high-dose cyclophosphamide. Oncology. 1999; 56:28-35.
18. Morrison VA, Picozzi V, Scott S, Pohlman B, Dickman E, Lee M, Lawless G, Kerr R, Caggiano V, Delgado D, Fridman M, Ford J, Carter WB; Oncology Practice Pattern Study Working Group. The impact of age on delivered dose intensity and hospitalizations for febrile neutropenia in patients with intermediate-grade non-hodgkin's lymphoma receiving initial CHOP chemotherapy: A risk factor analysis. Clin Lymphoma. 2001; 2:47-56.
19. Dixon DO, Neilan B, Jones SE, Lipschitz DA, Miller TP, Grozea PN, Wilson HE. Effect of age on therapeutic outcome in advanced diffuse histiocytic lymphoma: The Southwest Oncology Group experience. J Clin Oncol. 1986; 4:295-305.
20. Zinzani PL, Storti S, Zaccaria A, *et al*. Elderly aggressive-histology non-Hodgkin's lymphoma: First-line VNCOP-B regimen experience on 350 patients. Blood. 1999; 94:33-38.
21. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, Glick JH, Coltman CA Jr, Miller TP. A phase III comparison of CHOP *vs.* m-BACOD *vs.* ProMACE-CytaBOM *vs.* MACOP-B in patients with intermediate- or high-grade non-Hodgkin's lymphoma: Results of SWOG-8516 (Intergroup 0067), the National High-Priority Lymphoma Study. Ann Oncol. 1994; 5 (Suppl 2):91-95.
22. Dees EC, O'Reilly S, Goodman SN, Sartorius S, Levine MA, Jones RJ, Grochow LB, Donehower RC, Fetting JH. A prospective pharmacologic evaluation of age-related toxicity of adjuvant chemotherapy in women with breast cancer. Cancer Invest. 2000; 18:521-529.
23. Balducci L, Yates J. General guidelines for the management of older patients with cancer. Oncology (Williston Park). 2000; 14:221-227.

(Received May 8, 2010; Revised September 2, 2010; Accepted September 16, 2010)