Original Article

High Incidence of Febrile Neutropenia in Non-Hodgkin Lymphoma Patients Receiving CHOP Chemotherapy Despite G-CSF Prophylaxis

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Abstract:

Introduction: *The standard chemotherapy for Non-Hodgkin lymphoma (NHL) is CHOP-based regimens and the most important complication is febrile neutropenia (FN). Currently the addition of Rituximab to CHOP (R-CHOP) and G-CSF prophylaxis are commonly prescribed. Therefore, we aimed to determine the up-to-date incidence and risk factors of febrile neutropenia among Thai patients.* ***Method:*** *We conducted a retrospective and prospective cohort study. The NHL patients who received CHOP or R-CHOP regimens at King Chulalongkorn Memorial Hospital from 2006-2016 were followed for febrile neutropenia. G-CSF prophylaxis was given according to attending doctor discretions.* ***Results:*** *A total of 195 patients were enrolled. The median age was 61 years old and 52% were female. The incidence of febrile neutropenia was 25% (50/195). FN occurred in 22.5% (27/120) vs. 30% (23/75) of R-CHOP vs. CHOP groups, respectively (p = 0.20). The incidence among patients who received G-CSF prophylaxis was 26.7% (39/146). Without G-CSF prophylaxis, FN was found in 4.2% (1/24) of patients who were all young and had no risk factors. Multivariate analysis showed that age > 65 years (Odds ratio [OR] 2.77, 95% Confidence interval [CI]: 1.11-6.88, p 0.028) and the presence of comorbid diseases (OR 3.01, 95%CI: 1.21-7.45, p 0.017) could predict febrile neutropenia.* ***Conclusion:*** *In spite of G-CSF prophylaxis, the incidence of febrile neutropenia after R-CHOP or CHOP regimens was still high among Thai patients, especially the elderly with comorbid diseases.*

Keywords : ● *R-CHOP* ● *Febrile neutropenia* ● *G-CSF prophylaxis*

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นิพนธ์ต้นฉบับ

ภาวะไข้ร่วมกับเม็ดเลือดนิวโทรฟิลต่ำพบบ่อยในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กิน ที่ได้รับเคมีบำบัด CHOP แม้จะได้รับ G-CSF แบบป้องกัน

จิตติมา ปูชิตเสถียร และ พลภัทร โรจน์นครินทร์

สาขาโลหิตวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย และ โรงพยาบาลจุฬาลงกรณ์

บทคัดย่อ

ที่มา *การรักษาด้วยยาเคมีบำบัดสูตร CHOP ถือเป็นมาตรฐานในการรักษาผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิด นอนฮอดจ์กิน ภาวะแทรกซ้อนที่สำคัญคือการเกิดไข้ที่มีภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำ (Febrile neutropenia) ปัจจุบันได้มีการใช้ แอนตีบอดีต่อ CD20 (Rituximab) ร่วมในสูตรการรักษาและมีการใช้ G-CSF เพื่อป้องกันภาวะเม็ดเลือดขาวต่ำมากขึ้น โครงการวิจัยนี้มีวัตถุประสงค์เพื่อศึกษาถึงอุบัติการณ์การเกิดภาวะไข้ที่มีภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำในปัจจุบัน* ***วิธีการวิจัย*** *การศึกษาติดตามแบบไปข้างหน้า และย้อนหลังในผู้ป่วยมะเร็งต่อมน้ำเหลืองชนิดนอนฮอดจ์กิน ที่ได้รับยาเคมีบำบัด สูตร CHOP และ R-CHOP ในโรงพยาบาลจุฬาลงกรณ์ ระหว่าง 1 มกราคม พ.ศ. 2550 ถึง 1 มกราคม พ.ศ. 2559 การพิจารณาให้ G-CSF ขึ้นอยู่กับแพทย์ผู้รักษา* ***ผลการศึกษา*** *ผู้ป่วยที่เข้าร่วม 195 คน ผู้ป่วยร้อยละ 71.3 ได้รับ G-CSF หลังเคมีบำบัดครั้งแรก อุบัติการณ์การเกิดไข้ที่มีภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำคิดเป็นร้อยละ 25 (50/195) ของผู้ป่วยทั้งหมด กลุ่ม CHOP เกิดร้อยละ 30 (23/75) และ R-CHOP เกิดร้อยละ 22.5 (27/120, p = 0.020) กลุ่มที่ได้รับ G-CSF เป็นการป้องกันแบบปฐมภูมิเกิดไข้จากเม็ดเลือดขาวต่ำร้อยละ 26.7 (39/146) ส่วนในกลุ่มที่ไม่ได้รับเกิดเพียงร้อยละ 4.2 (1/24) โดยผู้ป่วยกลุ่มนี้ส่วนใหญ่มีอายุน้อย และไม่มีปัจจัยเสี่ยง จากการศึกษาแบบพหุตัวแปรพบว่าปัจจัยเสี่ยงที่สำคัญที่ทำให้เกิดไข้จากเม็ดเลือดขาวต่ำได้แก่อายุมากกว่า 65 ปี (Odds ratio [OR] 2.77, 95% Confidence interval [CI]: 1.11-6.88, p 0.028) และผู้ป่วยที่มีโรคอื่นร่วม (OR 3.01, 95%CI: 1.21-7.45, p 0.017)* ***สรุป*** *แม้มีการใช้ G-CSF เพื่อป้องกันการเกิดไข้ที่มีภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำจากการให้ยาเคมีบำบัดมากขึ้นในปัจจุบันแต่อุบัติการณ์การเกิดไข้จากเม็ดเลือดขาวต่ำในประเทศไทยยังสูง โดยเฉพาะในผู้ป่วยที่สูงอายุ และมีโรคร่วม*

คำสำคัญ ● *R-CHOP* ● *Febrile neutropenia* ● *G-CSF prophylaxis*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2560;27:45-55.

Introduction

The incidence of non-Hodgkin lymphoma (NHL) has been increasing worldwide. In 2011, 286,000 patients were treated as NHL around the world and 66,360 cases were newly-diagnosed in North America. This is attributed to 4.2% of all cancer.[1] The incidence of NHL in Thailand is also high, i.e., more than 1,000 new patients annually.[2]

Adding rituximab (monoclonal antibody to CD20) to conventional chemotherapy, such as the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) regimen is the current standard treatment in CD 20 positive B-cell non-Hodgkin lymphoma, due to an improvement in both overall and event free survival,[3-5] especially in diffuse large B cell lymphoma (DLBCL).[6]

Despite the improvement of overall survival (OS) and event free survival (EFS) in the rituximab era, serious complications are still problematic. Treatment-related mortality especially febrile neutropenia is still high.[7] In addition, most patients, who experience febrile neutropenia, have to receive reduced-dose or delayed chemotherapy that may affect the clinical outcomes especially the cure rate.[7,8]

Febrile neutropenia is defined as having a body temperature of more than 38.3˚C or more than 38.0˚C and persisting for one hour[9] plus neutropenia, absolute neutrophil count of lower than 0.5 x 10^9/L or lower than 1 x 10^9/L with a trend to be lower than 0.5 x 10^9/L in 48 hours.[9]

The European Organization for Research and Treatment of Cancer (EORTC) Guidelines 2010 stratified the risk groups of febrile neutropenia into high, intermediate and low risk groups. Patients receiving chemotherapy regimens having incidences of febrile neutropenia of more than 20%, between 10% and 20%, lower than 10% were stratified as high, intermediate and low risk group, respectively. The EORTC guidelines suggest that primary G-CSF prophylaxis should be used in the high risk group and secondary prophylaxis should be given in all who experience febrile neutropenia.[11] Primary G-CSF prophylaxis is defined as any administration of G-CSF during the first five days of the first cycle of chemotherapy and secondary G-CSF use is defined as G-CSF among patients with a history of a prior episode of febrile neutropenia.

Previous retrospective studies found different incidences of febrile neutropenia among non-Hodgkin lymphoma patients after chemotherapy with or without G-CSF ranging from 17 to 50% after CHOP[10] and approximately 19% after R-CHOP.[5,11] Therefore, febrile neutropenia incidence after CHOP was between the high and intermediate groups.

Moreover, studies have suggested other risk factors for febrile neutropenia other than the myelosuppressive effect of chemotherapy, such as age over 65 years, poor performance status, a high LDH level, bone marrow involvement of tumors, anemia, low serum albumin and presence of comorbid disease.[13-15] Therefore, physician decisions to use G-CSF must be individualized according to the patients' risk factors.

Intragumtornchai T and et al.[13] performed a prospective study of the incidence of febrile neutropenia in Thailand in 2000. They reported an incidence of 33% after the first CHOP regimen without G-CSF prophylaxis, which was much higher from other studies. This study was performed before the rituximab and G-CSF era and data were collected only in the first cycle. The incidence and risk factors of febrile neutropenia after G-CSF prophylaxis remain unclear in Thailand. This study aimed to investigate these questions and to determine clinical outcomes of patients experiencing febrile neutropenia. The results would be helpful in clinical practice for treating non-Hodgkin lymphoma patients in Thailand.

Material and Method

Study design and participants

This was a retrospective and prospective descriptive study performed at King Chulalongkorn Memorial Hospital (KCMH). We enrolled patients who were

diagnosed as non-Hodgkin lymphoma between January 2006, and January 2016. Searching was performed using electronic program by ICD10 code and the KCMH lymphoma registry. This study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University (IRB number 368/58).

Eligible patients were aged 15 years or older, had a diagnosis of non-Hodgkin lymphoma and received CHOP based regimen with or without rituximab. The miniCHOP regimen was not included. The decision to use G-CGF prophylaxis was left to treating physicians. Dose of G-CSF was 5 to 6 micrograms/kg started within 24 to 48 hours after chemotherapy administration. Duration of G-CSF was decided by the physicians. Cases with chemotherapy protocol changes or data losses were excluded.

Data collection included patient demographics, laboratory results before chemotherapy session, chemotherapy regimens, use of G-CSF and clinical courses with outcomes of febrile neutropenia.

Statistical analysis

The sample size was calculated as 195 subjects using the 15% estimated incidence of febrile neutropenia from literature review and 90% power at a two-sided significance level of 0.05.

The primary endpoint was the incidence of febrile neutropenia that is presented as percentage and 95% confidence interval (CI). Secondary endpoints were risk factors of febrile neutropenia using univariate and multivariate analyses. All statistical tests were based on a two-sided alpha level of 0.05. Other categorical data were calculated in frequency and percent. Continuous data are presented as means, standard deviations, medians and interquartile ranges (IQR). Statistical analysis was performed using SPSS version 17.

Results

Baseline characteristics

A total of 225 medical records met the eligible criteria. Twenty patients (8%) underwent chemotherapy regimen changes due to poor response or toxicity. An additional ten patients (4%) were excluded due to missing data.

After exclusion, 195 cases were included in the analysis. The use of rituximab depended on individual health coverage and financial status. Primary G-CSF prophylaxis was given in 146 (75%) of both CHOP and R-CHOP groups. In all, chemotherapy sessions totaled 1,151 cycles. The data were collected prospectively in 50 cases and retrospectively in 145 cases.

In this study, 102 of 195 patients (52.3%) were females. The mean age was 58 years (range 15 to 88 years, median 61 years, standard deviation 14.2). The patient diagnoses included diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, peripheral T-cell lymphoma and mantle cell lymphoma. The most common diagnosis was DLBCL, 69.6% (135/195). The second most common was FL, 17% (33/195). Fifty-five percent of patients showed high or high to intermediate international prognostic index (IPI). Thirty-five percent of patients had comorbid diseases such as diabetes, hypertension, chronic kidney disease, liver disease and cardiovascular disease. Diabetes was the most common comorbid disease (42%). Baseline characteristics are shown in Tables 1 to 3.

Incidence of febrile neutropenia

Twenty-five percent (50/195) of patients experienced febrile neutropenia. The rates were 30% in the CHOP and 22% in the R-CHOP group ($p = 0.20$). In the group receiving G-CSF prophylaxis, the incidence of febrile neutropenia was 26% (39/146). In the secondary G-CSF prophylaxis group, the incidence of recurrent episodes of febrile neutropenia was 25% (5/25). Notably, the incidence of febrile neutropenia was 4.2% (1/24) in the no G-CSF prophylaxis group. However, the no prophylaxis group showed significantly different baseline characteristics compared with the primary prophylaxis group. The baseline characteristics of each group are shown in Table 3.

There were six HIV positive cases with an FN incidence of 16% (1/6). In addition, there were two infections with ANC over 1 x 10^9/L; and therefore, did not fit the criteria for FN.

Characteristics of febrile neutropenia

A total of 50 patients (53 episodes) were hospitalized for febrile neutropenia. In all, 43 patients were admitted at KCMH and 7 patients were treated in other hospitals. A total of 11 patients had recurrent episodes of febrile neutropenia (22%). Of the 53 episodes reported in this group, the first event of febrile neutropenia occurred after the first, second, third, fourth, fifth and sixth cycles in 52%, 11%, 7%, 11%, 13% and 4%, respectively.

Septic work-up including hemoculture, urine culture and chest-X-ray in all patients yielded negative results among 50%. The positive cultures commonly showed *E. Coli* and *Klebsiella* spp. Some patients were contracted more than one organism. The most common source of infections was identified as the respiratory tract (26.4%), while urinary tract and gastrointestinal tract symptoms were noted among 16.9% in each group. Twenty-four percent had no organ specific symptoms (Tables 4 and 5).

The presence of fever most frequently occurred on rest day 8 after chemotherapy (40%). All patients were admitted with a median hospital length of stay of 7 days (range 2- 358 days). Thirty-six percent (18/50) experienced severe sepsis causing a mortality rate of 25% (10/50) contributing to 5% of all NHL patients (10/195). The complete blood count showed mean hemoglobin of 8.3 g/dL, absolute neutrophil count of 0.287 x 10^9/L and platelet count of 109.454 x 10^9/L

Risk factors associated with febrile neutropenia

Univariate analysis showed age more than 65 years, presence of comorbid diseases, previous chemotherapy, poor performance status, high IPI, presence of B symptoms and high LDH were significantly related to febrile neutropenia as shown in Table 6

Table 1 Baseline characteristics

Patient characteristics	No. of patients
Median (years)	61
Younger than 65 years	61.5% (120/195)
Sex	
- Female	52.3% (102/195)
Comorbidity	
- Present	35.2% (68/193)
Cell type	
- Diffuse large B cell lymphoma	69.6% (135/195)
- Follicular lymphoma	17% (33/195)
- Mantle cell lymphoma	4.1% (8/195)
- MALT lymphoma	2.6% (5/195)
- PTCL, NOS	1.5% (3/195)
- CLL	0.5%(1/195)
- Others	4.6% (9/195)
Stage	
- Stage 3-4	61.3% (117/191)
Performance status	
- ECOG 0-1	62.8% (120/191)
B-symptoms	
- Present	57.3% (110/192)
IPI	
- High risk	55.5% (106/191)
Rituximab	
- Receive (R-CHOP)	61.5% (120/195)
G-CSF	
- No	12.4% (24/194)
- Primary prophylaxis	75.3%(146/194)
- Secondary prophylaxis	12.4% (24/194)
Hemoglobin (mean)	11.7 g/dL
- > 12 g/dL	50.6% (97/192)
WBC	
- > 4 x 10^9/L	94.7% (182/192)
Platelet	
- > 100 x 10^9/L	95.8% (184/192)
Albumin (Mean)	3.82 g/dL
- Normal	77.8% (148/190)
LDH	
- High	56.3% (108/192)

MALT, Mucosa-associated lymphoid tissue; PTCL, NOS, Peripheral T cell lymphoma not otherwise specified; CLL, Chronic lymphocytic leukemia

Table 2 Baseline characteristics of CHOP and R-CHOP groups

Patient characteristics	CHOP (N = 75)	R-CHOP (N = 120)
Less than 65 year	58.7% (44/75)	63.3% (76/120)
Sex- female	38.5% (34/75)	56.7% (68/120)
Presence of comorbid disease	38.2% (26/75)	35.4% (42/118)
Pathological diagnosis		
- Diffuse large B cell lymphoma	70.3% (52/75)	69.2% (83/120)
- Follicular lymphoma	9.5% (7/75)	21.7% (26/120)
- Mantle cell lymphoma	5.4% (4/75)	3.3% (4/120)
- MALT lymphoma	2.6% (2/75)	2.5% (3/120)
- T cell lymphoma	2.6% (2/75)	0.8% (1/120)
- Chronic lymphocytic leukemia	1.4% (1/75)	0
- Others	8% (6/75)	2.5% (3/120)
Performance status ECOG 0-1	41.3% (44/75)	65.5% (76/116)
Presence of B symptom	73.3% (55/75)	53% (55/117)
Presence of extranodal disease	60% (45/75)	42.2% (40/116)
IPI- High risk	65.3% (49/75)	49.1% (57/116)
G-CSF No	16% (12/75)	10.1% (12/120)
Primary prophylaxis	70.3% (53/75)	78.3% (94/120)
Secondary prophylaxis	38.7% (10/75)	11.6% (14/120)
Hemoglobin (mean)	11.6 g/dL	11.7 g/dL
White blood cell count(mean)	7.687 x 10^9/L	7.689 x 10^9/L
Platelet count (mean)	269.860 x 10^9/L	267.200 x 10^9/L
Creatinine (mean)	0.85 mg/dL	0.85 mg/dL
AST/ALT (mean)	38/28 IU/L	31/29 IU/L
Albumin (mean)	3.8 g/dL	3.8 g/dL
- Normal	76.7% (56/73)	78.7% (92/117)
LDH- High	65.3% (49/75)	54.4% (59/117)
Response of treatment in first regimen		
Complete remission (CR)	60% (45/75)	74.2% (89/120)
Partial response (PR)	9.3% (7/75)	13.3% (16/120)
Stable disease (SD)	1.3% (1/75)	0% (0/120)
Progressive disease (PD)	6.6% (5/75)	1.6% (2/120)
Death from lymphoma	9.3% (7/75)	3.3% (4/120)
Death due to febrile neutropenia	6.6% (5/75)	4.2% (5/120)
Not evaluated	6.6% (5/75)	1.6% (2/120)
Relapsed rate	22% (10/45)	11.2% (10/89)

Table 3 Baseline characteristics of G-CSF primary prophylaxis and no prophylaxis groups

Patient characteristic	G-CSF (N = 146)	No G-CSF (N = 24)
Less than 65 year	56.8% (83/146)	75% (18/24)
Sex- female	52% (76/146)	54% (13/24)
Presence of comorbid disease	39% (57/146)	16% (4/24)
Pathological diagnosis		
- Diffuse large B cell lymphoma	67.1% (98/146)	70% (17/24)
- Follicular lymphoma	19.1% (28/146)	16% (4/24)
- Mantle cell lymphoma	4.1% (6/146)	4.1%(1/24)
- MALT lymphoma	2.7% (4/146)	0% (0/24)
- T cell lymphoma	1.3% (2/146)	4.1% (1/24)
- Chronic lymphocytic leukemia	0.6% (1/146)	0% (0/24)
- Others	4.6% (7/146)	4.1% (1/24)
Performance status ECOG 0-1	39.7% (58/146)	91.6% (22/24)
Presence of B symptom	58% (85/146)	41.6% (10/24)
Presence of extranodal disease	48% (71/146)	33.3% (8/24)
IPI- High risk	56.15% (82/146)	41.6% (10/24)
Rituximab	63.6% (93/146)	50% (12/24)
Hemoglobin (mean)	11.7 g/dL	11.6 g/dL
White blood cell count (mean)	7.972 x 10^9/L	7.996 x 10^9/L
Platelet count (mean)	268.403 x 10^9/L	268.550 x 10^9/L
Creatinine (mean)	0.85 mg/dL	0.85 mg/dL
AST/ALT (mean)	30.9/29 IU/L	31/29 IU/L
Albumin mean	3.82 g/dL	3.81 g/dL
- normal	75% (110/146)	75% (18/24)
LDH- High	45% (66/146)	41.6% (10/24)

Table 4 Sources of infection

Source of infection	Number of patients (N = 53)	Percent
Unknown	14	26.4
Respiratory tract (Pneumonia, bronchitis)	14	26.4
Urinary tract	9	16.9
Diarrhea	9	16.9
Skin and soft tissue	5	9.5
Bacteremia	1	2
Surgical wound	1	2

Table 5 Specific organisms

Organisms	Number of patients	Percent
No growth	27/53	50
E. Coli	9/53	16.9
Pseudomanas spp.	2/53	4
Klebsiella spp.	3/53	6
Aspergillosis	1/53	2
Others	7/53	13
More than 1 organism	4/53	7.5

Others: Proteus, pneumocystis, Streptococcus spp., *A. Baumannii*, *Enterococcus* spp., *Acinetobacter lwoffii*, More than one: Klebsiella+Aeromonas, Klebsiella+*E. Coli*+*C. difficile*, *E. Coli*+*H. Influenzae*+TB

Table 6 Univariate analysis of risk factors for febrile neutropenia

Risk factors	Odds ratio	95% Confidence interval	p value
Age over 65 years	2.65	1.37-5.10	0.003
Presence of comorbid disease	2.74	1.41-5.34	0.02
Presence of B symptom	2.58	1.25-5.27	0.008
Poor performance status	0.38	0.29-0.75	0.005
Advanced stage (III-IV)	2.29	1.10-4.77	0.024
High IPI	5.83	2.55-13.34	0.000
High LDH	2.73	1.33-5.57	0.005
Low albumin	0.33	0.16-0.73	0.03

Table 7 Multivariate analysis of risk factors for febrile neutropenia

Risk factors	All patients			Primary G-CSF prophylaxis		
	Adjusted OR	95%CI	p value	Adjusted OR	95%CI	p value
Age over 65 years	2.773	1.117-6.882	0.028	1.934	0.60-6.19	0.22
Presence of comorbid disease	3.012	1.217-7.456	0.017	6.63	1.95-22.48	0.002
Serum creatinine > 1.5 mg/dL	-	-	-	6.7	1.01-45.0	0.04

OR, Odds ratio; CI, Confidence interval

The significant variables identified by univariate analysis were further tested in multiple logistic regression (Table 7). Two factors found to be significantly associated with febrile neutropenia were age more than 65 years (Odds ratio [OR] 2.77, 95%CI: 1.11-6.88, p = 0.028) and presence of comorbid diseases (OR 3.01, 95%CI: 1.21-7.45, p = 0.017). Subgroup analysis also was conducted in the G-SCF primary prophylaxis group revealing that comorbid diseases and serum creatinine over 1.5 mg/dL were associated with higher incidence of febrile neutropenia (Table 7).

Among 75 patients older than 65 years, the incidence of febrile neutropenia was 38.1% (24/63) vs. 14.3% (1/7), in cases with vs. without G-CSF primary prophylaxis, respectively.

Discussion

Febrile neutropenia is a serious complication after receiving treatment for non-Hodgkin lymphoma using CHOP-based regimens. In this study, the incidence of febrile neutropenia was 25%. Adding rituximab to CHOP regimen did not increase the incidence of

febrile neutropenia compared with CHOP alone. Risk factors associated with febrile neutropenia were advanced age (over 65 years) and presence of comorbid disease. The protective effect of G-CSF could not be demonstrated in this study as the no G-CSF group had the lowest incidence of febrile neutropenia. Younger age, good performance status and absence of comorbidity in the no G-CSF group may explain this lower incidence.

The results presented here differed from those of Intragumtornchai T and et al.[13] showing a high incidence of febrile neutropenia of 33%. However, they collected data only after the first cycle, probably the highest incidence in all studies. Moreover, a related study was conducted in the pre-rituximab and G-CSF era. Related studies showed an incidence of febrile neutropenia after CHOP-based regimen (mostly R-CHOP) of 19 to 21%. This study showed a slightly higher incidence in Thailand of 25%. Subgroup analysis between CHOP and R-CHOP showed that the R-CHOP group revealed a lower incidence but without significance (22.5% vs. 30%). In addition, the CHOP group had more patients with advanced age (65.5% vs. 41.3%), presence of B symptoms (73% vs. 53%), presence of extranodal disease (76% vs. 42%), higher IPI (65.3% vs. 49.1%) and lower G-CSF primary prophylaxis (54.4% vs. 65.3%).

We found an incidence of febrile neutropenia in the G-CSF prophylaxis group of 26.7%. In contrast, the fit patients, comprising 12.4% of total cases, were not given G-CSF in all chemotherapy sessions and revealed a low febrile neutropenia incidence of 4.2%. Of note, 75% of this group were younger than 65 years and 86% had no underlying disease. The patients who experienced febrile neutropenia and were given G-CSF in the next chemotherapy cycle as secondary prophylaxis (24% of total case), showed recurrent episodes of febrile neutropenia in 25%, similar to that of the primary prophylaxis group. The effectiveness of G-CSF could not be demonstrated in this study because of the nonrandomized design. However, this study suggested that young patients without comorbidity may not require G-CSF prophylaxis. This could save costs in a limited resource country, such as Thailand.

The risk of febrile neutropenia was 2.8 times higher in the advanced age group and 3 times higher in the presence of comorbid diseases. The results did not differ from related studies. However, other variables showed no statistical significance. These comprised poor performance status, advanced stages[3-4], high IPI, presence of B-symptoms and elevated LDH. This may be due to a small sample size and/or data loss because of the retrospective design.

A subgroup analysis was conducted in G-CSF primary prophylaxis group revealing that the presence of comorbid diseases showed 6.6 times and serum creatinine level over 1.5 mg/dL showed 7.8 times increased risk of febrile neutropenia. Therefore, although this population was given G-CSF as primary prophylaxis, greater awareness of the risk of febrile neutropenia must be created in these two subgroups. Thus, decreased doses of CHOP such as miniCHOP should be considered to prevent febrile neutropenia.

In our study, organ specific infection was mostly found in the respiratory tract, urinary tract and gastrointestinal tract. The most common organisms were Gram negative bacteria, which did not differ from related studies.[22] Gram positive infections in neutropenic hosts are uncommon in Thailand. This may be because antibiotic primary prophylaxis; such as ciprofloxacin, is infrequently used. The mortality rate of febrile neutropenia was 20%. Among those who were admitted and had severe infections, the mortality rate was 36%. This study was not totally prospective. Therefore, risk factors for mortality regarding febrile

neutropenia, such as time to administered antibiotic, duration from fever to hospital visit, patient self-care and home environment could not be identified. Therefore, prospective studies should be performed. In the future, antibiotic prophylaxis may be considered to prevent the morbidity and mortality from serious infections among high risk patients receiving G-CSF.

In conclusion, this study analyzed the incidence of febrile neutropenia post CHOP in the rituximb and G-CSF era and also associated risk factors. Future studies are warranted to determine more risk factors, the efficacy of G-CSF prophylaxis and roles of antibiotic prophylaxis among patients who are at risk for febrile neutropenia.

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