Risk Factors for Neutropenia after the First Cycle of Chemotherapy for Non-Hodgkin Lymphoma

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ABSTRACT

Background and Objective: Neutropenia that occurs after the first cycle of chemotherapy for non-Hodgkin's Lymphoma (NHL) may predict its recurrence in the subsequent cycles. Moreover, it has also been reported to be a poor prognostic factor for the treatment outcome. Therefore, we aimed to observe the incidence of first cycle neutropenia and identify the potential risk factors for its occurrence among patients with NHL underwent chemotherapy.

Methods: A retrospective cohort was conducted in Sardjito General Hospital, Yogyakarta, Indonesia to analyze 466 subjects during 2012-2018, confirmed NHL, age 17 or older, treatment-naïve, underwent first-line chemotherapy without any previous primary GCSF prophylaxis. Relevant clinical conditions, pre-treatment laboratory parameters and treatment factors were obtained from medical records. Univariate and multivariate analysis were done using logistic regression to determine the significant factors.

Results: Among 466 NHL subjects, 241 (51.7%) received rituximab-containing regimen, with DLBCL as predominant subtype in 196 subjects (41.8%). Neutropenia occurred in 119 (25.5%; 95% CI 21.7-29.6%) of the cases, with 87 (73.2%) of them had moderate-severe neutropenia. Age older than 50 years old, use of rituximab-containing regimen, $ANC \leq 4.83 \times 10^3$ cells/mm³, and $WBC \leq 7.26 \times 10^3$ cells/mm³ were significant predisposing factors for first cycle neutropenia. A multivariate analysis showed two significant prognostic factors i.e., rituximab-containing regimen and ANC level $\leq 4.83 \times 10^3$ cells/mm³ with OR 2.18 (95% CI 1.38–3.43) and 2.30 (95%CI 1.49–3.57), respectively.

Conclusion: The administration of rituximab-based regimen and pre-treatment $ANC \leq 4.83 \times 10^3$ cells/mm³ in NHL require more attention to anticipate the occurrence of neutropenia after the first chemotherapy cycle. Further investigation is required to validate risk model and identify subgroup who benefits from early use of growth factor.

Keywords: ANC, first cycle, neutropenia, Non-Hodgkin's Lymphoma (NHL), rituximab.

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I. INTRODUCTION

Combination chemotherapy is an essential treatment modality for non-Hodgkin lymphoma (NHL), mainly intermediate- to high-grade lymphoma [1]. CHOP regiment which consists of cyclophosphamide, doxorubicin, vincristine, and prednisone has been a standard of care for aggressive lymphoma for a long time, particularly Diffuse Large B-Cell Lymphoma (DLBCL). After rituximab era, the regiment which was later known as R-CHOP regiment has brought substantial improvement in terms of 10 years overall survival (OS) from 27.5% to 43.5% among older patients with DLBCL (60-80 years old) and 3 years OS from 84% to 93% in younger patient [2], [3].

Despite achieved successful story of CHOP and later R-CHOP regiment, myelotoxicity complication for this regiment in terms of neutropenia is still relatively high, with neutropenia incidence reported at minimum 20% for CHOP [4]. Moreover, the incidence of severe neutropenia with R-CHOP is reported to be higher than CHOP for more than 50%, with 40% of them later progressed into febrile neutropenia [5], [6]. Febrile neutropenia would predispose the patient to receive suboptimal relative dose intensity (RDI) and lead to unplanned hospitalization with longer length of stay [7]. Moreover, suboptimal chemotherapy later contributes to inferior survival in NHL and frequent hospitalization with longer stay means a high charge in economic cost [5], [7].

Most studies reported a predominantly higher neutropenia incidence, particularly severe neutropenia, and febrile neutropenia in the first cycle of chemotherapy for CHOP and R-CHOP regiment [6]-[8]. Identical to a cascade, patients who experienced febrile neutropenia would have greater risk for neutropenia complication in subsequent cycle which has been confirmed for NHL with CHOP regiment [9]. The absolute neutrophil count (ANC) nadir observed after received first cycle of chemotherapy may predict the occurrence of any neutropenia in subsequent cycles which means that the lower first cycle ANC nadir may predict a higher probability of neutropenia in next cycles [9], [10]. Furthermore, the first cycle neutrophil count nadir could predict overall survival (OS) in DLBCL which the most inferior 5-year OS would be experienced by patients with evidenced grade 4 neutropenia after receiving first cycle of chemotherapy [11]. Eventually, the incidence of first cycle neutropenia in NHL warrants to be investigated, and any risk factors for its occurrence need to be determined.

Pretreatment parameters either clinical or laboratory that had been reported to predict subgroup with higher risk of neutropenia, including older age, poorer performance status (ECOG >1), any multiple comorbidities, bone marrow infiltration and lower baseline peripheral blood count that may reflects insufficient bone marrow reserve which promotes retention of WBC components in bone marrow via stromal-cell-derived factor 1 (SDF-1) [5], [8], [12]-[14]. Thus, our study aims to report the incidence of first cycle neutropenia in NHL and identify any potential risk factors either from clinical or laboratory factors from our patients' study population.

II. METHODS

A. Study Design and Patient Selection

Six hundred sixty-one (661) patients were confirmed as NHL and registered in the hospital registry in Sardjito General Hospital during January 2012 – December 2018. Inclusion criteria were age of 17 years old or older, confirmed NHL, treatment-naïve, did not receive primary Granulocyte colony-stimulating factor (G-CSF), and received the first line chemotherapy. Exclusion criteria included incomplete clinical and laboratory data. Ethical approval of the study was obtained from ethical committee of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada.

A cohort of 466 subjects fulfilled the inclusion and exclusion criteria were analyzed further. Clinical information was abstracted from medical record and converted into case report form. Nadir point of neutrophil count would be followed from patient laboratory result to assess the severity of neutropenia occurred during day 7 or earlier in day 21 after administration of the first chemotherapy.

B. Covariates of Neutropenia: Clinical and Pretreatment Laboratory Parameters

Clinical factors considered as covariate of neutropenia from previous studies [8], [15], [16] were included in the analysis, such as age, Ann-arbor stage, performance status, body mass index (BMI), and relative dose intensity (RDI) of regiment. RDI was calculated from the ratio of actual dose given divided with the fore planned dose to the patient. Only cyclophosphamide and anthracycline were included for RDI calculation- due to their potent myelosuppression effects- according to Hryniuk methods [5], [7], [17], [18]. Nutrition status was presented with body mass index and classified using Asia-Pacific BMI (WHO/IASO/IOTF, 2000). Pretreatment laboratory parameters were also generated from medical records, including hemoglobin level (Hb), white blood count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), LDH, and albumin.

C. Neutropenia Outcome

Neutropenia was defined as $ANC < 1500 \text{ cells/mm}^3$ and the severity of neutropenia was classified as mild neutropenia ($1000 - < 1500/\text{mm}^3$), moderate ($500 - < 1000/\text{mm}^3$), and severe ($< 500 \text{ cells/mm}^3$) [16], [19]. First cycle neutropenia was a condition which fulfilled criteria of neutropenia and occurred during 7th day or earlier to 21 days after chemotherapy [20].

D. Statistical Analysis

Potential covariate of first cycle neutropenia was evaluated using univariate logistic regression for parameter with nominal scale, meanwhile numerical data including blood count was analyzed using Mann-Whitney test or independent t-test, based on normality. Any significant different laboratory parameter between neutropenia and non-neutropenia subject would be subsequently analyzed for their optimum cut-off point using receiver operating curve (ROC). Later, previously significant numerical laboratory data was classified into categorical data using optimum cut-off point and analyzed with binary logistic regression. Degree of association between any covariates and the occurrence of first

cycle neutropenia would be presented with odd ratio (OR). Any significant covariate with univariate analysis would be continued into multivariate analysis to obtain the adjusted OR. P-value < 0.05 would be considered statistically significant. Statistical analysis was performed using SPSS version 25.0 and MedCalc version 18.0.

III. RESULTS

A. Baseline Characteristics

A number of 466 NHL subjects underwent first-line chemotherapy were evaluated, with 241 (51.7%) of them received rituximab-containing regiment (R-CHOP or R-CEOP). Median age of patient was 55 years old with male to female ratio was 1.6:1. Clinical stage was predominantly limited in 364 subjects (78.3%) with a large portion of the subjects, 195 patients, were DLBCL (41.8%); although 93 subjects (20%) could not be specified in terms of their subtype due to limited immunohistochemical study. Most of the subjects, 84.5% or 394 of subjects were in good ECOG performance status. Elevated LDH were found in 54% or 159 subjects. Despite most of subjects were in normal nutrition status, 109 subjects or 23.7% were underweight. Values of blood count components, presented in median, for hemoglobin, platelet, white blood count, ANC, ALC, and AMC, all were within normal range.

TABLE I: BASELINE CHARACTERISTICS OF SUBJECTS

Parameter N = 466	Frequency (%)
Age median (range)	55 (17–85)
Sex	
Male	269 (57.7%)
Female	197 (42.3%)
Ann Arbor Stage	
1	228 (49.2%)
2	136 (29.1%)
3	74 (15.9%)
4	28 (6.0%)
ECOG Performance Status	
0-1	394(84.5%)
2 or more	72(15.5%)
LDH (n = 159)	
High	87 (54.7%)
Normal	72 (45.3%)
BMI / Nutritional Status (n = 460)	
Underweight (<18.5)	109 (23.7%)
Normal (18.5 - <23)	200 (43.5%)
Overweight (23 - <25)	123 (26.7%)
Obese (≥25)	28 (6.1%)
NHL Subtype	
Diffuse Large B Cell Lymphoma	195 (41.8%)
Follicular Lymphoma	17 (3.6%)
Anaplastic Large Cell Lymphoma	6 (1.3%)
Burkitt Lymphoma	4 (0.9%)
Small Lymphocytic Lymphoma	10 (2.1%)
Other NHL B Cell Lymphoma	96 (20.6%)
T Cell Lymphoma, NOS	42 (9.0%)
MALT Lymphoma	3 (0.6%)
NHL, NOS	93 (20.0%)
Regiment Received	
CHOP / CEOP	199 (42.7%)
R-CHOP / R-CEOP	241 (51.7%)
COP/R-COP(Non-anthracycline)	23 (4.9%)
Other Regiments	3 (0.7%)
Hemoglobin median (interquartile range)	12.5 (11.2–13.6)
WBC median (interquartile range)	7.8 (6.33–9.80)
ANC median (interquartile range)	5.02 (3.77–6.83)
ALC median (interquartile range)	1.67 (1.14–2.28)
AMC median (interquartile range)	0.58 (0.43–0.79)

B. Incidence and Severity of First Cycle Neutropenia

Neutropenia occurred in 119 patients with the incidence of first cycle neutropenia of 25.5% (95% CI 21.7-29.6%). The incidence and severity of first cycle neutropenia among NHL patients is displayed in Fig 1. Most of them were within moderate to severe neutropenia, which occurred in 87 patients or 73.2% of neutropenia patients.

Fig. 1. Incidence and severity of first cycle neutropenia among NHL subjects (n = 466).

C. Predictor of First Cycle Neutropenia in Non-Hodgkin Lymphoma

Univariate analysis for the clinical and treatment factors of the first cycle neutropenia is described in Table II. Patient age was dichotomized with a cut-off of 50 years old according to the younger median of subjects and the optimum cut-off from ROC analysis between age and the first cycle neutropenia (graph is not shown). Age and rituximab-containing regiment were shown to have a higher risk of first cycle neutropenia (OR 1.59 (95% CI 1.03-2.52 and OR 2.18 (CI 95% 1.39-3.40), respectively). Other factors, such as sex, clinical stage, extra nodal involvement, LDH level, BMI and RDI did not have any significant association with the first cycle neutropenia ($p > 0.05$).

Pretreatment laboratory parameters between neutropenia and non-neutropenia subjects in univariate analysis is shown in Table III. Subjects with first cycle neutropenia had significantly lower median pretreatment WBC and ANC (p -value 0.012 and 0.005, respectively). Other laboratory parameters such as ALC, AMC, platelet count, hemoglobin level, and albumin did not show any significant difference in both groups. Subsequent analysis was done for WBC and ANC to dichotomize both parameters based on ROC analysis (graph is not shown), resulted in $ANC \leq 4.83 \times 10^3$ cells/mm³ and $WBC \leq 7.26 \times 10^3$ cells/mm³ as cut-off point.

Univariate analysis resulted that age older than 50 years old, use of rituximab-containing regiment such as R-CHOP or R-CEOP, $ANC \leq 4.83 \times 10^3$ cells/mm³, and $WBC \leq 7.26 \times 10^3$ cells/mm³ were significant to predispose for the occurrence of the first cycle neutropenia in NHL. However, multivariate analysis evidenced that only rituximab-containing regiment and ANC level $\leq 4.83 \times 10^3$ cells/mm³ were the predictors of first cycle neutropenia among NHL subjects with respective OR 2.18 (95%CI 1.38-3.43) and 2.30 (95%CI 1.49-3.57), as shown in Table IV.

TABLE II: UNIVARIATE ANALYSIS FOR CLINICAL FACTOR BETWEEN NEUTROPENIA AND NON-NEUTROPENIA SUBJECTS

Patient Characteristics		Neutropenia (n = 119)		Non-Neutropenia (n = 347)		p value	OR (95% CI)
		N	Row N %	N	Row N %		
Age	Age > 50 yo	87	28.4%	219	71.6%	0.047*	1.59 (1.03–2.52)
	Age ≤ 50 yo	32	20.0%	128	80.0%		
Clinical Stage	Advanced Stage	24	23.8%	77	76.2%	0.674	0.90 (0.54–1.50)
	Limited Stage	94	25.8%	270	74.2%		
Extranodal Sites	2 or more	11	27.5%	29	72.5%	0.766	1.12 (0.54–2.31)
	0-1 site	108	25.4%	318	74.6%		
ECOG	ECOG ≥ 2	13	18.1%	59	81.9%	0.113	0.60 (0.32–1.14)
	ECOG 0-1	106	26.9%	288	73.1%		
LDH (n = 159)	High LDH	22	25.3%	65	74.7%	0.967	1.02 (0.49–2.09)
	Normal LDH	18	25.0%	54	75.0%		
BMI	Underweight	33	30.3%	76	69.7%	0.307	Reference 1.41 (0.84–2.39)
	Normal	47	23.5%	153	76.5%		
	Overweight	32	26.0%	91	74.0%		
Regiment	Obese	4	14.3%	24	85.7%		0.54 (0.18–1.64)
	With Rituximab	80	33.2%	161	66.8%	0.001*	
	Without Rituximab	37	18.6%	162	81.4%		2.18 (1.39–3.40)
Relative Dose Intensity (RDI)	Median (IQR)	95.95 (99.85 – 79.13)		93.40 (82.30 – 98.70)		0.248	

*Significant with binomial logistic regression (p<0.05).

TABLE III: UNIVARIATE ANALYSIS OF PRE-TREATMENT LABORATORY PARAMETER BETWEEN NEUTROPENIA AND NON-NEUTROPENIA SUBJECTS

Parameter	Neutropenia (N = 119)	Non-Neutropenia (N = 347)	P-value
	Median (Interquartile Range)	Median (Interquartile Range)	
WBC	7,100 (6,030–9,370)	7,980 (6,500–10,050)	0.012*
ANC	4,440 (3,600–6,520)	5,260 (3,950–6,980)	0.005*
ALC	1,580 (1,130–2,050)	1,700 (1,400–2,360)	0.233
AMC	540 (400–790)	600 (450–790)	0.216
Platelet Count	298,000 (227,000–364,000)	306,000 (235,000–375,000)	0.201
Hb	12.5 (11.2–13.5)	12.5 (11.2–13.7)	0.769
Albumin	3.85 (3.20–4.23)	3.97(3.38–4.40)	0.435

*Significant with binomial logistic regression (p < 0.05).

TABLE IV: UNIVARIATE AND MULTIVARIATE ANALYSIS FOR PREDICTORS OF FIRST CYCLE NEUTROPENIA IN NHL

Patient Characteristics	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (> 50 years, ≤ 50 years)	1.59 (1.03–2.52)	0.049		
Regiment (R-CHOP /R-CEOP, CHOP/CEOP)	2.18 (1.39–3.40)	0.001	2.18 (1.38–3.43)	0.001*
ANC (≤ 4.83, > 4.83) × 10 ³	2.14 (1.49–3.26)	<0.001	2.30 (1.49–3.57)	<0.001*
WBC (≤ 7.26, >7.26) × 10 ³	1.85 (1.22–2.82)	0.004		

*Significant with backward LR logistic regression (p < 0.05)

IV. DISCUSSION

There were 119 from 466 patients (25.5%) experienced first cycle neutropenia with degree of moderate to severe neutropenia in 87 patients (18.7%). Although many studies investigating the incidence of neutropenia have varying definitions of neutropenia, this study has quite similar results in accordance with Nadeem *et al.* [4] that reported neutropenia incidence for 19.9% with severe neutropenia occurred in 16.6% of all subjects involved in that study [4]. On the other hand, other study reported a relatively high incidence of severe neutropenia in cycle 1 (53%) compared with this study (9.87%) among NHL patients [8]. A high disparity of severe neutropenia incidence observed in the former study may be attributed by relatively older patients (mean age of 66 years old) involved in a previous study. A recent meta-analysis also confirmed a linear trend of increasing age in the incidence of neutropenia (OR 1.39; CI 1.11–1.76), not only among NHL cases, but also among other solid cancers such as breast cancer, non-small cell lung cancer, colorectal, and gynecological cancer [21]. However, in this study, age-related factor (> 50 years old) was significantly affected neutropenia events only in univariate analysis (OR 1.59; CI 1.03–2.52), but not in multivariate

analysis.

Previously, it was assumed that the administration of the rituximab with CHOP (R-CHOP) did not affect the incidence of first-cycle neutropenia compared with regiment without rituximab [8]. However, our retrospective data suggested an increased risk of first-cycle neutropenia in subjects given rituximab compared to those without monoclonal antibody therapy (OR 2.18; CI 95% 1.38–3.43). Another retrospective study reported a 23% of febrile neutropenia among B-cell NHL patients received R-CHOP without primary GCSF prophylaxis and a lower incidence of 7.3% among subjects receiving GCSF prophylaxis. Although the incidence of severe neutropenia or febrile neutropenia were not analyzed directly, a clinical trial compared R-CHOP with CHOP in elderly DLBCL patients demonstrated a higher median nadir of neutrophil count in the CHOP group than in the R-CHOP group [3]. A relatively higher incidence of neutropenia with rituximab might be contributed by the production of antibodies against neutrophils, resulting in neutropenia. Other theories included aberrant B-cell reconstitution, disturbance of granulocyte by chemokine stromal-derived factor-1 (SDF-1) interacting with B-lymphocyte recovery, and polymorphisms in the immunoglobulin G (IgG) Fc receptor (FcγR) [22]. Other study suggested that rituximab-induced neutropenia is likely to be asymptomatic and is unlikely to be

associated with fatal infection due to its short occurrence [23]. However, this notion could not be confirmed in this study.

Pretreatment laboratory had been reported to predict the risk of neutropenia, including lower baseline peripheral blood count that may reflects a relatively low bone marrow reserve and a limiting amount of endogenous GCSF [5], [8], [9]. Thus, it might promote retention of WBC components in bone marrow via stromal-cell-derived factor 1 (SDF-1) [12]-[14]. However, it still requires further studies to confirm and validate this hypothesis. In our data, a lower pretreatment white blood count (WBC) ($\leq 7.26 \times 10^3$ cells/mm³) and lower absolute neutrophil count (ANC) ($\leq 4.83 \times 10^3$ cells/mm³) were two significant pretreatment laboratory parameters related with first cycle neutropenia in the univariate analysis, albeit only lower ANC remained significant prognostic factor in the multivariate analysis. Both parameters represent marrow reserve which are very susceptible to be affected by myelosuppressive agents used in the treatment of NHL and rituximab, similar with previous studies [8], [9], [12], [14].

In conclusion, the analysis of our study population identified several clinical and pretreatment laboratory factors that correlated with the incidence of first cycle neutropenia. Older age (>50 years) and lower pretreatment white blood count (WBC) ($\leq 7.26 \times 10^3$ cells/mm³) should raise awareness and caution in the treatment of DLBCL, particularly when accompanied with the use of rituximab and lower absolute neutrophil count (ANC) ($\leq 4.83 \times 10^3$ cells/mm³).

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CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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