

Non-Hodgkin's Lymphoma in Jakarta

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ABSTRACT

Aim : To see the characteristics of Non Hodgkin's Lymphoma patients in Jakarta. Methods: The retrospective design was used in this research. Sample were Non Hodgkin Lymphoma patients who treated in Cipto Mangunkusumo National Hospital and "Dharmais" National Cancer Center Hospital during 2004-2005. Results: Seventy eight percent of NHL patients were at the age of bellow sixty years old with male gender predominant (60.8%), stage I-II (68.97%) and good performance status (ECOG 0-1, 86.67%). Based on exposure evaluation, eighty percent patients were unknown. Out of 153 patients, 94 patients were treated by CHOP regimen, only 51 patients who complete the minimal six cycles of regimen. The response to treatment on this group were : complete remission (52.38%), partial remission (26.19%), and minimal response (14.2%).

In the CHOP group of treatment, we reported that eighty percent of NHL patients were at the age of bellow sixty years old with early stage (stage I-II, 74.47%) and good performance status (ECOG 0-1, 93.3%). Also reported that ninety percent patient had ≤ 1 extranodal involvement and normal LDH level (60%). Based on pathology results in CHOP group of treatment, fifty three percent patients were Diffuse Large B Cell (DLBCL) NHL.

Conclusion: NHL patients characteristics in Jakarta predominantly were bellow sixty years old with male gender, early stage and good performance status. Based on CHOP group of treatment, we reported also a bellow sixty years old patients with early stage and good performance status. Fifty percent patients in the CHOP group of treatment had complete remission after minimal six cycle of chemotherapy

Keyword: Non Hodgkin Lymphoma, performance study, remission

ABSTRAK

Tujuan: Melihat karakteristik pasien Limfoma Non Hodgkin di Jakarta. Metode: studi retrospektif. Sampel adalah pasien Limfoma Non Hodgkin yang berobat di RS Cipto Mangunkusumo dan RSK "Dharmais" antara tahun 2004-2005.

Hasil: Tujuh puluh delapan persen pasien memiliki usia kurang dari 60 tahun dengan gambaran mayoritas jenis kelamin laki-laki, stadium awal (60,8%) dan status performans yang baik (ECOG 0-1; 86,67%). Berdasarkan evaluasi terhadap paparan, didapati delapan puluh persen pasien tidak diketahui paparannya.

Dari 153 pasien, 94 pasien diobati dengan kemoterapi regimen CHOP, namun hanya 51 pasien yang menyelesaikan minimal 6 siklus kemoterapi. Dilaporkan juga respon terhadap terapi adalah: remisi komplit (52,38%), remisi parsial (26,19%) dan respon minimal (14,2%).

Pada kelompok pasien yang diobati dengan regimen kemoterapi CHOP, dilaporkan bahwa delapan puluh persen pasien berusia di bawah 60 tahun, memiliki stadium awal (stadium I-II; 74,47%) dan status performans yang baik (ECOG I-II; 93,3%). Juga dilaporkan bahwa sembilan puluh persen pasien memiliki ≤ 1 keterlibatan ekstranodal dan kadar LDH normal (60%). Berdasarkan hasil patologi, dilaporkan lima puluh persen pasien memiliki gambaran patologi DLBCL (Diffuse Large B Cell L).

Kesimpulan

Sebagian besar pasien Limfoma Non Hodgkin di Jakarta memiliki karakteristik klinis: usia di bawah 60 tahun dengan jenis kelamin laki-laki, stadium awal dan status performans yang baik. Pada kelompok pasien yang menjalani kemoterapi regimen CHOP juga dilaporkan karakteristik klinis yang sama. Lima puluh persen pasien yang menjalani kemoterapi regimen CHOP mencapai respon komplit setelah menjalani minimal 6 siklus kemoterapi.

Kata kunci : Limfoma Non Hodgkin, Performa studi, remisi

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INTRODUCTION

The term of lymphoma describes a heterogeneous group of malignancies, which are divided into two large groups of neoplasms, namely Non Hodgkin's Lymphoma and Hodgkin disease. About 90% of all malignant lymphomas are Non Hodgkin's Lymphomas (NHL).¹⁻³

The incidence of NHL had increased dramatically since 1970 and continues to raise at the rate of 5-10% each year. It reached five most frequent malignant diseases in America with 12-15 cases per 100,000 people, accounting for 4% of all malignancies.⁴ National Cancer Institute, in 1996, reported the incidence of NHL in America was 15.5 per 100,000 people. In Indonesia, NHL along with Hodgkin disease and leukemia ranks as the sixth most frequent diseases. Along with the increase of NHL incidence, its mortality rates continues to increase.⁵ In 1997, NHL was reported as a major malignant cause of death of male patients at the age 29-30 years. In the year 2000, it was reported in America that there were 54,900 new cases and 26,100 of them died. In 2001, NHL was found as the fourth leading cause of cancer deaths.⁶ There is still no explanation for the increasing incidence of NHL. Close association between AIDS and NHL may highlight the uncertain link between NHL and infection.⁷⁻⁹ We still need to conduct further research to look for possible explanation for the increasing number of the NHL's incidence.

Surveillance Epidemiology and End Result (SEER) in United States of America reports that the median age at diagnosis for NHL is 67 years old and rarely happens in children or adolescence. However, it can be found at all age.^{5,10,11} NHL is found more frequent in male with the incidence 19 per 100,000 people than in female, 12 per 100,000 people.¹¹

Non-Hodgkin's Lymphoma (NHL) originates from the lymphoid tissues. It represents a group of primary lymphocyte malignancy, which evolves from B cell, T cell or Natural Killer (NK) cell within the lymphatic system. This group of disease shows different varieties of histological appearances, clinical pictures, responses to therapy and prognosis.¹⁻³

The diagnosis of NHL based on history, physical examination, laboratory studies and additional investigations. However, different varieties of NHL clinical manifestations have made early diagnosis difficult to make. Most patients are more likely to be asymptomatic, especially in indolent NHL.¹¹ Therefore, the diagnosis of NHL relies on pathological confirmation following appropriate tissue biopsy. In addition to histopathological examination, recent studies has demonstrated the significance of using modern techniques such as immunohistochemistry and immunophenotyping, which

are found to be sensitive and specific in diagnosis and classification of NHL.^{12,13} Nevertheless, more research is needed to attribute the significance of these modern techniques in the making if NHL diagnosis.

Twenty-one days CHOP regimen has been the standard treatment for patients with NHL and should be given every three weeks for 3-6 cycles. Some literatures stated that treatment can be given in two weeks (fourteen days) if necessary.¹⁴ Delay of treatment is allowed for one week, nonetheless, it is not stated regarding the maximum number of treatment delay for a patient that still can give good result. Subsequently, literatures stated that if the treatment were delivered accurately, a complete remission would reach 80% of all patients given CHOP regimen. Salvage regimen is given to the patients experiencing relapse.¹⁵ Meanwhile, for the patients proved unresponsive or estimated to be less responsive, some centers would choose to perform bone marrow transplant. Recent studies have reported better results in the addition of rituximab to the CHOP regimen.^{11,16,17}

Objectives: There are no sufficient and reliable data regarding epidemiologic study in NHL patients receiving CHOP regimen in Indonesia. Meanwhile, the need of preliminary study in this field is essential to provide valuable reports for further research.

Therefore, the objective of the study is to see the epidemiology of Non Hodgkin's Lymphoma in Indonesia, particularly in Jakarta.

MATERIAL AND METHODS

Our epidemiological study was conducted in Jakarta, Indonesia. The method that used was a retrospective research in NHL patients receiving chemotherapy treatments in Cipto Mangunkusumo National Hospital and "Dharmais" Cancer Hospital during 2004-2005.

RESULTS

Basic Characteristics

The NHL demographic data in Indonesia is presented in table 1. It is shown that 117 patients (78%) of 153 NHL patients in our study were at the age of less than sixty years old. The table also shows a higher incidence on male than female.

There were no specific preferences among patients race. Of 153 patients, 35 patients (22.9%) were each Javanese and Betawi, 23 patients (15%) were Sundanese, 7 patients were Batak (4.6%), 6 patients (3.9%) were Chinese, 5 patients (3.3%) were Padang and 42 remaining patients (27.5%) were classified in Others. Exposure also seems to show no specific preferences. One hundred and twenty eight patients (83.8%) were having NHL without unknown exposures. However, 17 patients (11%) were exposed to cigarette consumption, 3 patients (2%) were

Table 1: Basic characteristics

Characteristic	N	%
Age		
< 60 years old	117	78
> 60 years old	33	22
Sex		
Male	93	60.8
Female	60	39.2
Race		
Java	35	22.9
Sundanese	23	15.0
Batak	7	4.6
Padang	5	3.3
Betawi	35	22.9
Chinese	6	3.9
Others	42	27.5
Exposure		
Chemicals	3	2
Cigarette	17	11
Radiation (non UV)	1	0.7
Ultraviolet (sunlight)	3	2
Hair Toning	1	0.7
Unknown	128	83.8
Family History of Cancer		
Yes	1	7
No	29	19
Unknown	123	80.4
ECOG		
0 & 1	91	86.67
2,3 & 4	14	13.33
Staging		
I – II	100	68.97
III, IV	44	30.34
Relapse	1	0.67
LDH		
Normal	50	59.52
High	34	40.48

exposed to chemicals, 3 patients (2%) were exposed to ultraviolet (sunlight), 1 patient (0.7%) was exposed to radiation (non UV) and 1 patient (0.7%) was exposed hair toning. Our study also shows that 123 patients (80.4%) had unknown family history of cancer, 29 patients (19%) had no family history of cancer and only one patient (7%) had family history of cancer.

Ninety-one patients (86.67%) showed ECOG performance status of 0 and 1, while the remaining 14 patients (13.33%) showed *Eastern Cooperative Oncology Group* (ECOG) performance status of 2, 3 and 4. Approximately more than half of all patients were at early stage I – II (68.97%), and had normal level of LDH (59.52%).

Clinical Characteristic

Of 153 patients, 59 patients (38.56%) have not been treated. Ten patients (6.54%) each have entered first and second cycle of CHOP treatment. Eleven patients (7.19%) have entered the third cycle, 4 patients (2.61%) have entered the fourth cycle, 8 patients (5.23%) have entered the fifth cycle, 42 patients (27.45%) have entered the sixth cycle, 2 patients (1.31%) have entered the seventh cycle, 6 patients (3.92%) have entered the eighth cycle.

Table 2: Frequency of CHOP treatment

Frequency of treatment	N	%
0	59	38.56
1	10	6.54
2	10	6.54
3	11	7.19
4	4	2.61
5	8	5.23
6	42	27.45
7	2	1.31
8	6	3.92
13	1	0.65
Total	153	100.00

Table 3: Treatment response of minimally 6 cycles CHOP

Type of response	Number of treatment Frequency	%
Complete Response	22	52.38
Partial Response	11	26.19
Minimal Response	6	14.29
Relapse	3	7.14
Total	42	100.00

* Unavailable data: nine patients

Out of 153 patients, 51 patients were treated with minimally six cycles of CHOP with response to treatment showed in table 3.

The response to treatment of this group shows 22 patients with complete remission (52.38%), 11 patients with partial remission (26.19%), and six patients (14.29%) with minimal response. Three patients (7.14%) were progressive during treatment and there were nine patients (17.65%) with unavailable data. We also tried to compare the feature between CHOP and non CHOP group of chemotherapy regimen.

In comparison between patients receiving CHOP as chemotherapy regimen and patients not receiving CHOP as chemotherapy regimen, the majorities in both groups were at age less than 60 years old, had ECOG performance status score 0 and 1, had normal level of

Table 4: Clinical and laboratory feature of patient with and without CHOP as chemotherapy regimen

Variables	Results	
	Non CHOP (%)	CHOP (%)
Age		
• ≤ 60 years old	117 (78)	41 (80.4)
• > 60 years old	33 (22)	10 (19.6)
ECOG		
• 0 & 1	91 (86.67)	42 (93.3)
• 2, 3 & 4	14 (13.33)	3 (6.67)
LDH		
• Normal	50 (59.52)	18 (60)
• High	34 (40.48)	12 (40)
Extra nodal Involvement		
• ≤ 1 locations	136 (89.47)	46 (90.2)
• > 1 locations	16 (10.53)	5 (9.8)
Stadium		
• I or II	100 (68.97)	35 (74.47)
• III or IV	44 (30.34)	12 (25.53)
• Relapse	1 (0.67)	0
Pathology Result		
• Diffuse Large B Cell NHL*	41 (45.6)	16 (53.33)
• Large Centroblastic B Cell NHL	4 (4.44)	1 (3.33)
• Large B Cell Lymphoma, Variant T Cell Rich*	1 (1.11)	1 (3.33)
• Large B Cell NHL*	9 (10)	5 (16.67)
• Diffuse Large B Cell Lymphoma Var. Centroblastic*	2 (2.22)	0
• B Cell Lymphoma*	3 (3.33)	1 (3.33)
• Mantle Cell Lymphoma, Diffuse Large B Cell^	1 (1.11)	1 (3.33)
• Mantle Cell Lymphoma^	1 (1.11)	1 (3.33)
• Blastoid Mantle Cell Lymphoma^	1 (1.11)	0
• Follicular B Cell#	4 (4.44)	1 (3.33)
• Diffuse Follicle Center Lymphoma	2 (2.22)	0
• Follicular Lymphoma Grade 2#	1 (1.11)	0
• Follicular Lymphoma Grade 1#	2 (2.22)	1 (3.33)
• T/NK Cell Lymphoma Nasal Type	1 (1.11)	0
• NK/TCL Lymphoma+	6 (6.67)	2 (6.67)
• T Cell NHL	6 (6.67)	0
• Small Lymphocytic NHL	2 (2.22)	0
• Small B Cell NHL	1 (1.11)	0
• Monocytoid B Cell Lymphoma	1 (1.11)	0
• Inflammation reaction	1 (1.11)	0

LDH, had less than one extra nodal involvement and were stages I or II. Table 4 shows that 14 patients not receiving CHOP (13.33%) have ECOG score two, three and four. Moreover, on patients receiving minimally 6 cycles of CHOP, only three patients (6.67%) have ECOG score above one.

The elevated LDH was identified as a negative prognostic factor and normal LDH shows good prognosis.

There are 34 patients (40.47%) with high level of LDH on patients who were not treated with CHOP and only 12 patients (40%) with high level of LDH on patients who were treated with 6 cycles of CHOP chemotherapy. However, there are 50 patients (59.52%) with normal level of LDH in the group who were not receiving CHOP and there are 18 patients (60%) in the group who were receiving CHOP.

At first we concluded that most patients were admitted in advanced stage, thus, the treatment was showing poor response. Nevertheless, it shows only 44 patients out of 145 patients not receiving CHOP (30.35%) who were advanced stages (III or IV). In the group of patients treated with 6 cycles of CHOP, only 12 patients (25.53%) were admitted in stages III or IV. This does not support our conclusion.

Based on pathology result, most cases from patients treated with or without CHOP are diffuse large B cell NHL. Other form with frequent incidence after the diffuse large B cell NHL is large B cell NHL.

Immunohistochemistry study in all patients and patients treated with 6 cycles of CHOP shows that there are more than 60% patients have aggressive lymphoma. It is then considered that this factor reasons the patients' poor response to CHOP regimen therapy. The causal relationship between them is still yet to be explained, thus, further research is needed to elaborate the relation between aggressive lymphoma with poor response to CHOP regimen.

Three multicenter studies consisting of ECOG (*Eastern Cooperative Oncology Group*), SWOG (*Southwest Oncology Group*), and GELA (*Groupe d'Etude des Lymphomes de l'Adulte*) each showed complete response and or partial response after 8 cycles of CHOP 61%, 73%, 89% respectively. GELA study also showed complete and partial response subsequently using these regimen; COP (44%&36%), Mbacod (48% & 34%), *Pro MACE/Cytabom* (56%&31%), and *Macod B* (51%&32%).

Study conducted in France in 2003 which compared the use of CHOP and more aggressive ACBVP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) showed that ACBVP was more superior than CHOP as first line regimen for aggressive lymphoma or poor prognosis case, based on event-free survival (39% vs. 29%) and overall survival (46% vs. 38%), though with much higher level of toxicity. Meanwhile, in complete response patients, the use of ACBVP has quite similar result with use of CHOP (58% vs. 56%).

CONCLUSION

NHL patients characteristics in Jakarta predominantly were below sixty years old with male gender, early stage and good performance status. Based on CHOP group of

treatment, we reported also a bellow sixty years old patients with early stage and good performance status. Fifty percent patients in the CHOP group of treatment had complete remission after minimal six cycle of chemotherapy

We recommend for a better research design to be able to identify all prognostic factors, evaluate the treatment until the fourth cycle and immediately substitute the CHOP regimen therapy on patients who do not show complete remission. This is due to the correlating data that showed more than 60% of patients have high aggressive lymphoma, that they would need much stronger and more aggressive regiment. ❖

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