A Comparative Study of Early Response Rate between Patient Given Standard Chemotherapy with Patient Given Combination Targeted Therapy in Non-Hodgkin Lymphoma Patients

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Abstract

Background: Treatment for non-Hodgin Lymphoma (NHL) with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been standard chemotherapy regimens for treatment of patients with diffuse large B cell lymphoma and follicular lymphoma. Rituximab, a chimeric monoclonal antibody against the CD20 B-cell antigen. Rituximab in combination with CHOP (RCHOP) increases better response rate without any significant increase in toxicity. The standard definition of treatment responseis based on changes in lesion dimensions with time. We conducted a comparative study to compare early response rate between CHOP andCHOP in NHL patients.

Method: This study was using cohort prospective analysis and conducted at Wahidin Sudirohusodo Hospital from September 2018 until June 2019. The response rate was measured with the longest diameter of tumor and compared after 2 observational cycle periods of chemotherapy. Analysis to compare responserate was carried out using Independent T-test analysis.

Results: Seventy patients enroll this study consisting of 38 subjects in CHOP group and 32 subjects in RCHOP group. Analysis to compare early responserate between CHOP and RCHOP was significant with p-value 0.001 (46.6% vs 67.0%;).

Conclusions: Early response rate in patient given combination targeted therapy have better response rate than patient given standard regiment chemotherapy.

Keywords: *Early ResponseRate, RCHOP, CHOP, non-Hodgkin Lymphoma.*

Background

Malignant lymphoma is divided into 2 large groups of neoplasms namely Hodgin Lymphoma (HL) which characterized by presence of reed sternberg cells and non-Hodgin Lymphoma (NHL) which characterized by a collection of abnormal lymphocytes.[1,2] Non-Hodgin's lymphoma represent 80-90% of all malignant lymphoma.[3,4,5]. The most frequent type of NHL isdiffuse large B cell lymphoma (DLBCL), accounts for approximately 40% of lymphoma new cases.[6, 7] In Indonesia, NHL along with Hodgkin disease and leukemia ranks as the sixth most frequent diseases.[3, 8]

The management of NHL depends on several things including histophatological type, stage, differentiation, progression, age and patient's general condition.[3,9]

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Combination chemotherapy of cyclophospamide, doxorubicin, vincristin, prednison (CHOP) has emerged as the standard therapy for agrresive type of NHL for more than two decades.[7] Randomized studies had shown that CHOP is a chemotherapy that has same effectiveness with other regimens but has minimal toxicity.[7] Rituximab, a monoclonal antibody that binds specifically to CD20 antigen, which is expressed on the B lymphocytes surfaces.[7] Rituximab is given to NHL patients with positive CD20.[10] Various multicenter studies showed that rituximab combination with CHOP (RCHOP) increased survival rate and completed remission in first-line chemotherapy of DLBCL patients compared to CHOP alone.[6,11]

The first widely-used standard response categories for malignant lymphoma in the CT imaging erawere usingthe Cotswolds criteria.[12] Moreover, the most commonly used nowadays is NHL International Workshop Response criteria.[13] These standard definitions of treatment response are based on changes in lesion dimensions with time.[14] CT assessment of lymphoma after one or two cycles of chemotherapy may show some tumor shrinkage but the response was usually incomplete at that stage, especially tumors in larger size.[13,14] The studies on responserate comparing RCHOP with CHOP in NHL patientsand factors that influenced the responseratewere limited. Based on these findings, it is tempting to conduct the study especially in Makassar, Indonesia.

Method

This study used a prospective cohort design for patients with NHL who underwent chemotheraphy at Wahidin Sudirohusodo Hospital in Makassar from September 2018 to June 2019. Research subjects is population that meets research inclusion criteria. Patients were eligible if they wereabove eightteen years of age and histopathological examination showed non-Hodgin Lymphoma.All subjects provided written informed consent. Subjects were excluded if they wereusing other chemotherapy regimens besides CHOP and RCHOP or had obtaining radiotherapy during observation period.Subjects were drop out if have not completed 2 chemotherapy cyclesduring observation period.

We divided the subjects into 2 groups. The CHOP group weresubjects who received cyclophospamide, doxorubicin, vincristin, prednisoneand andthe RCHOP group were subjects who received rituximab addition to CHOP with a positive CD 20. Age was divided into groups by age <60 years and ≥60 years. Performance status was grouped into ECOG 0, I, II, III, IV. Subjects were grouped into without or with presenceof B symptoms if there was weight loss, excessive sweating and fever without other causes. Serum LDH was grouped into less than upper limit normal (ULN) (<220 U/L) and greater than ULNor equal to ULN (LDH ≥ 220 U/L). Ann Arbor stage consisting of stages I, II, III, IV. Subjects were grouped bulky disease (maximal tumordiametergreater than 7 cmor greater than one-third of internal transverse diameter of posterior-anteriorchest radiograph) or without bulky disease. Prognostic risk based on IPI Score is grouped into ; low risk: score 0-1, moderate risk: score 2, moderate-high risk: score 3 and high risk: score 4-5.

Earlyresponse rate was assessed based on changes in size of tumor before and after 2 chemotherapy cycles. If tumors more than one, we used the Sum of Longest Diameters (SLD) comparison. Tumors that can be assessed on body surface were assessed using a caliper while tumors located in internal organs of the body and involving extra nodules are assessed with radiology (chest X-ray or CT Scan).

Findings: Descriptive data analysis was performed on 70 subjects, CHOP group were 38 subjects (54.3%) and RCHOP group were 32 subjects (45.7%). This study consisted of male (61.4%) and female (38.4%). The age range of subjects was between 19-79 years with an average 50 ± 14 years, based on age was divided into <60 years (74.3%) and ≥60 years (25.7%). Serum LDH were grouped into less than ULN (24.3%) and greater than ULN or equal to ULN (75.7%).Immunohistochemical examination in this study subjects were 46 subjects with positive CD 20 (65.7%) and with negative CD 20 were 24 subjects (34.3%). B symptomspresenced in 32 subjects (45.7%) and absensed in 38 subjects (54.3%). Based on Ann Arbor stage, stage 1 (45.7%), stage 2 (17.1%), stage 3 (22.9%) and stage 4 (14.3%). Bulky disease presentedin study were 16 subjects (22.9%) and absense of bulky disease were 54 subjects (77.1%). Performance status with ECOG 1 (68.9%) and ECOG 2 (31.4%). Prognosisrisk which had low risk (50%), moderate risk (31.1%), and moderate risk (12.9%). (Table 1).

Table 1. Basic Characteristics

Variable	Characteristic	n	%
Chemotherapy	CHOP	38	54.3
	RCHOP	32	45.7
Gender	Male	43	61.4
	Female	27	38.6
Age	<60 years old	52	74.3
	≥60 years old	18	25.7
Serum LDH	Less than ULN	17	24.3
	Greater than ULN or equal to ULN	53	75.7
CD20	Positive	46	65.7
	Negative	24	34.3
B Symptoms	Presense	32	45.7
	Absense	38	54.3
Ann Arbor Stage	1	32	45.7
	2	12	17.1
	3	16	22.9
	4	10	14.3
Bulky Disease	Yes	16	22.9
	Not	54	77.1
Performance Status (ECOG)	1	48	68.6
	2	22	31.4
Prognosis Risk (IPI score)	Low	35	50.0
	Intermediate	26	37.1
	High-Intemediate	9	12.9

Histopathological features of anatomic pathology examination showed that Diffuse Large B Cell Lymphoma was the highest percentage with 26 subjects (37.1%), non-specific Hodgkin Lymphoma with 25 subjects (35.7%), Small Lymphocytic Lymphoma with15 subjects (21.4%), Follicular Lymphoma with 2 subjects (2.9%), Malignant Lymphoma Intermediate Cell with 1 subject (1.4%), and MALT Lymphoma with1 subject respectively (1.4%). (Table 2)

Table 2. Histopathological Features

Histopathological features	n	%
Diffuse Large B Cell Lymphoma	26	37.1
non-specific Hodgkin's lymphoma	25	35.7
Small Lymphocytic Lymphoma	15	21.4
Follicular Lymphoma	2	2,9
Malignant lymphoma Intermediate Cell	1	1,4
MALT Lymphoma	1	1,4
Total	**70**	**100.0**

The RCHOP group showed a better earlyresponse rate based on tumor size shrinkage percentage compared to CHOP group(67.0% vs 46.6%) significantly with p value 0.001. (Table 3).

Table 3. Comparison ofearlyresponserate of standard chemotherapy therapy with combination targeted therapy

Chemotherapy	n	Mean of early response	Standard devation	p-value
CHOP	38	46.6	26.2	0.001
RCHOP	32	67.0	21.8	

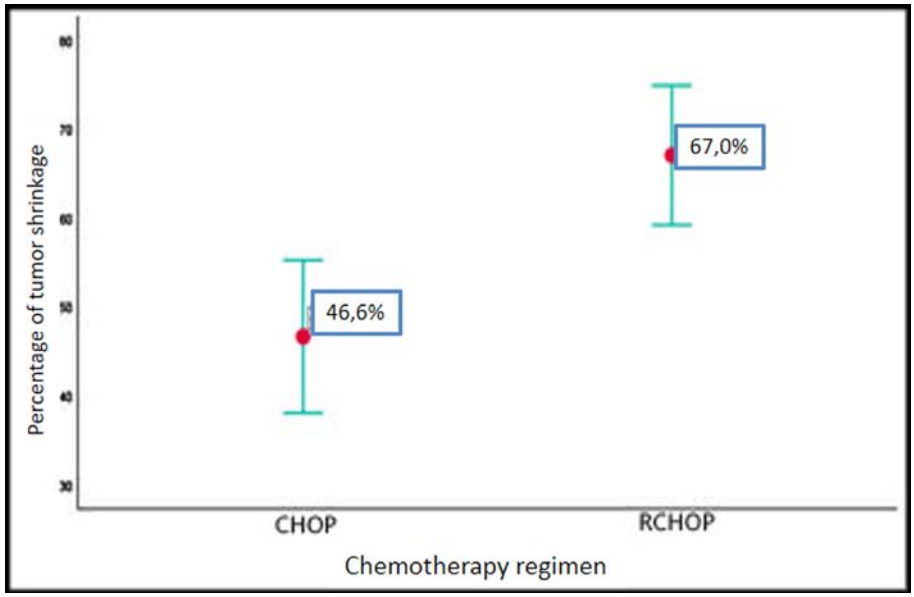

Figure 1. The comparison of early response rate between CHOP and RCHOP

Discussion

In this study, numbers of male subjects more than female subjects with a ratio of 1.6: 1, this is in line with the Intragumtornchai et al study, in 4056 patients with ratio of men than women 1.3: 1 and according to WHO data, in the United States ratio of male to female patients was 1.5: 1.[15,16] The age range of subjects in this study was 19-79 years with an average 50 ± 14 years. This is in accordance with subjects in study by Itragumtornchai et al with range of 16-99 years with an average age of 56 years.[15] Based on histopathological features in this study found that the highest prevalence was DLBCL, this is consistent with the data from WHO that among the malignancies of NHL, DLBCL was the highest prevalence of subtype.[17] Most aggressive lymphoma is DLBCL and its prevalence continue to increase by 3-4% every year.[18] We found that more patients had LDH serum greater than ULN. These result in accordance with study of Kasir et al that found all of the subjects hadLDH serumgreater than ULN.[19] LDH serum is prognostic factor and can be monitored to assess response rate.[20] Analysis in B limphocytes showed thatmost NHL have a positive CD20, but some of previous studied found that to 1-2% patients had negative CD20.[21] Based on B symptom, in this study 54.3% of subjects showed anabsense of B symptoms, according to previous NHL study that B symptoms were more common in aggressive lymphoma (41%) than in indolent lymphoma (19%).[22]

The RCHOP group showed better early response rate when compared to CHOP group (67.0% vs 46.6%; p=0.001). This study results were in line with studies by Delgado et al found that combination Rituximab with CHOP improvedcomplete response (CR) and delayed disease progression in folicular lymphoma patients.[23] In the same study, in DLBCL group the combination Rituximab showed no significant difference in long-term outcome.[23] Coifier et al study, found that patients who received 8 RCHOP chemotherapy cyclesgroup showed better CR number than CHOP group (76% vs 63%, P <0.05).[6] In addition to Nishimori et al study in Japan,patients who received 3-4 cycle of standard chemotheraphy regimen showed a greater CR difference in RCHOP group compared CHOP group (77.7% vs 69.4%, p<0.01).[7] Rituximab has an important role in calcium channels for B cell survival.[24] Complement-dependent cytotoxicity and human FC receptors are activated which trigger cellular antibody toxicity of cellular when rituximab which binds to CD20 receptor.[24] Rituximab mediates immune system and induces apoptosis.[24]

Conclusion

Early responserate in patients given combination targeted therapies showed better responserate than patients given standard regiments of Chemotherapy.

Conflict of Interest: No Potential conflict of interest relevant to be declared.

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Ethical Clearance: The study has been permitted and acknowledged by Hasanuddin University Ethic Medical Committee. Before each interview, each participant was given written information on the study. Each participant was also informed that his or her participant was voluntary. Before each interview, we emphasized the importance of maintaining confidentiality in relation to patient cases. All participants provided written consent to participate in this study.

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