

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

by Rahmawati Minhajat

Submission date: 28-Mar-2021 08:18AM (UTC+0700)

Submission ID: 1544019654

File name: Rahmawati_M_A_comparative_study_of_eraly_response.pdf (1.37M)

Word count: 2693

Character count: 14329

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

Ardan Miraz¹, Andi Fachruddin Benyamin², Tutik Harjianti²,
Rahmawati Minhajat², Syakib Bakri¹, Hasyim Kasim¹, Harun Iskandar¹

¹Internal Medicine Department, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia, ² Medical Hematology and Oncology Division of Internal Medicine Department, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia

Abstract

Background: Treatment for non-Hodgkin 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 response is based on changes in lesion dimensions with time. We conducted a comparative study to compare early response rate between CHOP and RCHOP 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 response rate 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 response rate 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 regimen chemotherapy.

Keywords: Early Response Rate, RCHOP, CHOP, non-Hodgkin Lymphoma.

Background

Malignant lymphoma is divided into 2 large groups of neoplasms namely Hodgkin Lymphoma (HL) which

characterized by presence of reed sternberg cells and non-Hodgkin Lymphoma (NHL) which characterized by a collection of abnormal lymphocytes.^{1,2} Non-Hodgkin's lymphoma represent 80-90% of all malignant lymphoma.^{3,4,5} The most frequent type of NHL is diffuse 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 histopathological type, stage, differentiation, progression, age and patient's general condition.^{3,9}

Corresponding Author:

Ardan Miraz

Internal Medicine Department, Hasanuddin University,
Hasanuddin University Hospital 5th Floor, Perintis
Kemerdekaan Road Km. 11, Makassar 90245, South
Sulawesi, Indonesia
e-mail: miraz.ardan@gmail.com

Combination chemotherapy of cyclophosphamide, doxorubicin, vincristin, prednisone (CHOP) has emerged as the standard therapy for aggressive 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 era were using the 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 response rate comparing RCHOP with CHOP in NHL patients and factors that influenced the response rate were 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 chemotherapy 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 were above eighteen years of age and histopathological examination showed non-Hodgkin Lymphoma. All subjects provided written informed consent. Subjects were excluded if they were using other chemotherapy regimens besides CHOP and RCHOP or had obtaining radiotherapy during observation period. Subjects were drop out if have not completed 2 chemotherapy cycles during observation period.

We divided the subjects into 2 groups. The CHOP group were subjects who received cyclophosphamide,

doxorubicin, vincristin, prednisone and the 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 presence of 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 ULN or equal to ULN (LDH ≥ 220 U/L). Ann Arbor stage consisting of stages I, II, III, IV. Subjects were grouped by disease (maximal tumor diameter greater than 7 cm or greater than one-third of internal transverse diameter of posterior-anterior chest 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.

Early response 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 symptoms presented in 32 subjects (45.7%) and absented 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 presented in study were 16 subjects (22.9%) and absence of bulky disease were 54 subjects (77.1%). Performance status with ECOG 1 (68.9%) and ECOG 2 (31.4%). Prognosis risk 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-Intermediate	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 with 15 subjects (21.4%), Follicular Lymphoma with 2 subjects (2.9%), Malignant Lymphoma Intermediate Cell with 1 subject (1.4%), and MALT Lymphoma with 1 subject respectively (1.4%). (Table 2)

Table 2. Histopathological Features

topathological 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 early response 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 of early response rate of standard chemotherapy therapy with combination targeted therapy

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

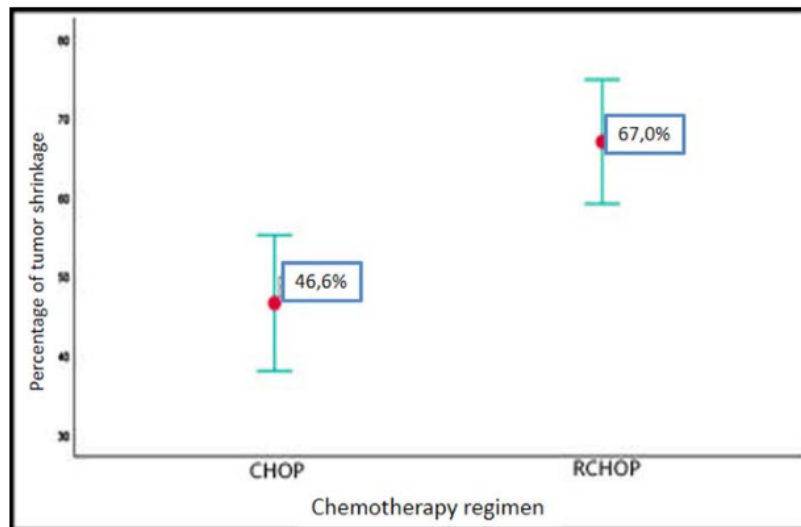


Figure 1. The comparison of early response rate between CHOP and RCHOP

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 ² patients had LDH serum greater than ULN. These result in accordance with study of Kasir et al that found all of the subjects had LDH serum greater than ULN.¹⁹ LDH serum is prognostic factor and can be monitored to assess response rate.²⁰ Analysis in B lymphocytes showed that most 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 an absence 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 ¹⁸ 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 improved complete response (CR) and delayed disease progression in follicular lymphoma patients.²³ In the same study, in DLBCL group the combination Rituximab showed no significant difference in long-term outcome.²³ Coiffier et al study, found that patients who received 8 RCHOP chemotherapy cycles group 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 chemotherapy regimen showed a greater ¹⁹ 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 responder rate in patients given combination targeted therapies showed better responder rate than patients given standard regimens of Chemotherapy.

⁷ **Conflict of Interest:** No Potential conflict of interest relevant to be declared.

² **Source of Funding:** This study was conducted with self funding, no external funding sources for this study

Ethical Clearance: The study has been permitted and acknowledged ¹ 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.

References

1. Bakta IM. Limfoma maligna. dalam: Hematologi Klinik Ringkas. Denpasar; 2006. 192–219.
2. Komite Penanggulangan Kanker Nasional. Panduan Penatalaksanaan Limfoma Non Hodgkin. Jakarta; 2016. 1-9.
3. Indonesian Ministry of Health Basic Health Research: Infodatin-Limfoma 2015. Infodatin. 2015. 1–6.
4. Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. *Lancet*. 2012; 380 (9844): 848–57.
5. Batra R, Kaur H, Jindal S. Extranodal large B-cell type aggressive non-Hodgkin's. *Indian Journal of Dentist*. 2014; 5 (4): 225–8.
6. Coiffier B, Eric L, Josette B. et al. Rituximab Vs CHOP alone in elderly patients with diffuse large B cell lymphoma. *N Eng J Med*. 2002; 346 (4): 235-42.
7. Nishimori H, Matsuo K, Maeda Y, et al. The effect of adding rituximab to CHOP-based therapy on clinical outcomes for Japanese patients with diffuse large B-cell lymphoma: A propensity score matching analysis. *Int J Hematol*. 2009; 89 (3): 326–31.
8. Reksodiputro AH. Limfoma non hodgin (LNH). dalam :Buku Ajar Ilmu Penyakit Dalam Alwi I, editor. Jakarta; 2014: 2980.

9. Huang HQ. Practice guidelines for the diagnosis and treatment of follicular lymphoma in China. *Cancer Bio Med.* 2013; (3): 36–42.
10. Dotan E, Aggarwal C, Smith MR. Impact of Rituximab (Rituxan) on the Treatment of B-Cell Non-Hodgkin's Lymphoma. *P & T.* 2010; 35 (3): 148-57.
11. Ren YR, Jin YD, Zhang ZH, et al. Rituximab treatment strategy for patients with diffuse large B-Cell lymphoma after first-line therapy: a systematic review and meta analysis. *Chin Med J (Engl).* 2015; 128 (3): 378.
12. Lister TA, Crowther D, Sutcliffe SB et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J ClinOncol.* 1989; 7: 1630-6.
13. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of hodgkin and non-hodgkin lymphoma: The lugano classification. *J Clin Oncol.* 2014; 32 (27): 3059–67.
14. Macmanus MP, Seymour JF, Hick RJ. Overview the early response assesment in lymphoma with FDG-PET. 2007. *Cancer Imaging*; 7: 10-18
15. Intragumtornchai T, Bunworasate U, Wudhikarn K, T, et al. Non-Hodgkin lymphoma in South East Asia: An analysis of the histopathology, clinical features, and survival from Thailand. *Hematologycal Oncology.* 2017; 1-9.
16. Teras LR, Desantis CE, Cerhan JR, et al. 2016 US Lymphoid Malignancy Statistics by World Health Organization Subtypes. *Ca Cancer J Clin.* 2016; 66 (6): 443–59.
17. Reksodiputro AH, Irawan C, Hardjolukito E, et al. Non-Hodgkin Lymphoma in Jakarta. *Indonesian Journal of Cancer.* 2011; 5 (3): 1–5.
18. Lunning M, Vose JM. Management of indolent lymphoma: where are we now and where are we going. *Blood Rev.* 2012; 26 (6): 279-88.
19. Kasir DR, Wahid I, Bachtiar H. Artikelpenelitian; Hubungan kadar laktat dehidrogenase dengan stadium limfomamaligna non hodgkindi Rumah Sakit Dr M. Djamil Padang periode Desember 2009 sampai Maret 2013. *Jurnal Kesehatan Andalas.* 2014; 3 (2): 128–30.
20. Yadav C, Ahmad A, Souza BD, et al. Serum lactate dehydrogenase in Non-Hodgkin's Lymphoma: A Prognostic Indicator. *Indian J ClinBiochem.* 2016; 31 (2): 240–2.
21. Katchi T, Liu D. Diagnosis and treatment of CD20 negative B cell lymphomas. *Biomarker Research.* 2017; 1–5.
22. Solal CP, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood.* 2019; 104 (5):1258–66.
23. Delgado GJ, Almaguer D, Arzaga LC, et al. Is there a benefit to adding rituximab to CHOP in the overall survival of patients with B-cell non-Hodgkin's lymphoma in a developing country? *Hematology.* 2012; 17 (4): 193–7.
24. Badin F, Hayslip J. Rituximab in the treatment of B-cell non-Hodgkin lymphoma, focus on outcomes and comparative effectiveness. *Clin Outcomes Res.* 2010; 2 (1): 37–45.

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

ORIGINALITY REPORT

16%

SIMILARITY INDEX

13%

INTERNET SOURCES

13%

PUBLICATIONS

6%

STUDENT PAPERS

PRIMARY SOURCES

1	annals-general-psychiatry.biomedcentral.com Internet Source	2%
2	Rasdiana Rasdiana, Faridin HP, Fardah Akil, AM Luthfi Parewangi et al. "Correlation between Uric Acid and Non-Alcoholic Steatohepatitis (NASH) Occurred in Obesity and Non-Obesity", Global Journal of Health Science, 2020 Publication	2%
3	repo.uum.edu.my Internet Source	1%
4	Submitted to Taibah University Student Paper	1%
5	www.science.gov Internet Source	1%
6	journal.unhas.ac.id Internet Source	1%
7	www.ijsrp.org	

Internet Source

1%

8

www.bloodjournal.org

Internet Source

1%

9

Submitted to University of Birmingham

Student Paper

1%

10

Hisakazu Nishimori, Keitaro Matsuo, Yoshinobu Maeda, Yuichiro Nawa et al. "The effect of adding rituximab to CHOP-based therapy on clinical outcomes for Japanese patients with diffuse large B-cell lymphoma: a propensity score matching analysis", International Journal of Hematology, 2009

Publication

1%

11

Submitted to Universitas Hasanuddin

Student Paper

1%

12

Bertrand Coiffier. "CHOP Chemotherapy plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma", New England Journal of Medicine, 01/24/2002

Publication

1%

13

umpir.ump.edu.my

Internet Source

1%

14

worldwidescience.org

Internet Source

<1%

15 repub.eur.nl Internet Source <1%

16 silo.pub Internet Source <1%

17 Lígia Barbosa Torres, Daniel Torres, Ana Cardoso. "Non-Hodgkin Lymphoma Presenting as Tonsillitis", Journal of Medical Imaging and Case Reports, 2020
Publication <1%

18 Ritsuko Seki, Koichi Ohshima, Koji Nagafuji, Tomoaki Fujisaki et al. "Rituximab in combination with CHOP chemotherapy for the treatment of diffuse large B cell lymphoma in Japan: a retrospective analysis of 1,057 cases from Kyushu Lymphoma Study Group", International Journal of Hematology, 2010
Publication <1%

19 lib.bioinfo.pl Internet Source <1%

20 repositorio.unesp.br Internet Source <1%

Exclude quotes On

Exclude bibliography On

Exclude matches

< 5 words