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Rector of YSMU

Armen A. Muradyan

Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37410) 580840 Editor-in-Chief

Fax: (+37410) 582532

E-mail: namj@ysmu.am

URL: http//www.ysmu.am

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Phone: (+374 55) 020627,
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CONTINUING MEDICAL EDUCATION (PKB) XXXIV INTERNAL MEDICINE
THE INDONESIAN SOCIETY OF INTERNAL MEDICINE (PAPDI) SURABAYA BRANCH
IN CONJUNCTION WITH
TRIGONUM SUDEMA MEETING INTERNAL MEDICINE 2019

"INTERNAL MEDICINE: CURRENT MANANGMENT IN DAILY PRACTICE"

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JI. Mayjend. Prof. Dr. Moestopo 6-8 Surabaya 60286
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About AIM-ICME

Introduction and description: Join us in Surabaya this coming March for a special edition of Continuing Medical Education XXXIV of Internal Medicine. Continuing Medical Education is an annual event launches by the Indonesian Society of Internal Medicine (PAPDI) Surabaya Chapter in collaboration with Faculty of Medicine Universitas Airlangga and RSUD dr. Soetomo.

The spotlight of this event will be Current Management in Daily Practice, highlighting not only latest updates on management of daily internal medicine cases from almost all major subjects in the field, but also how to manage them in escalated health care setting and when to refer. We will also focus on updating knowledge on how to launch a research.

We expect more than 700 delegates with more than 30 national and international speakers to showcase more than 20 scientific sessions during this three-day conference. All accepted scientific texts will also get benefit from national and international media exposure with SCOPUS indexed.

We look forward to welcoming you in Surabaya this coming March 2019. This is surely one professional event you cannot afford to miss. Learn, exchange, and update your skills on this coming event.

AIM & Scope:

Health care professionals worldwide are working with various health care system and facilities nowadays. It is necessary for all health care professionals to suit their skills and knowledge to work in this progressing healthcare situation and various facilities. It is the objective of this event to update and improve professional knowledge on how to overcome boundaries in such healthcare setting for the best patient management. We also aim to stimulate health care professionals on launching researches with our scientific program.

This international event brings together internists, cardiologists, pulmonologists, general practitioners, nurses, medical students, paramedics, and other allied professionals. The program will offer in-depth presentations by leading experts in almost all major subjects in daily internal medicine cases.

Chairman of Organizing Committee

Prof. ***Ummi Maimunah***, MD

Internist, Gastroenterology and Hepatology Consultant.

Honorable guests, participants, and respected colleagues.

Once again, it is the right moment successfully to immerse an incredible year's work. Considering how busy your job or activity as researcher, lecturer, student or else must be, it is an honour for us for having you as participant in the Annual Airlangga Internal Medicine-Continuing Medical Education (AIM-ICME) event in conjunction with Surabaya-Denpasar-Malang Trigonum Symposium launched by the Indonesian Society of Internal Medicine Surabaya in collaboration with Faculty of Medicine Universitas Airlangga and Dr. Soetomo Teaching Hospital Surabaya.

I welcome all of participants and wish that today's event will provide as an impetus for intensify the knowledge about management of daily internal medicine cases from approximately every major subjects in the field and their management in heighten health care setting.

We at Universitas Airlangga have continued to pursue the interdisciplinary research which in recent years have become common concern of famed universities around the world. As has been widely announce through press inclusion or coverage, Universitas Airlangga has already developed into a world-class university especially in research and publication. Universitas Airlangga is courageously innovating its system to become a global pilot of university or higher education and research implementation.

In addition to academic research and the education of talented individuals, the two goals unique to universities, Universitas Airlangga has been faithful to its role as a transmitter of knowledge that extends the fruits of its creative academic achievements and innovations in all sectors, including medical science. The existence of this Airlangga Internal Medicine-Continuing Medical Education (AIM-ICME) likewise is an expression of our will to leap even further as an innovative research pathfinder. By directly taking a closer look to studies by many excellent academia, we expect to contribute even more directly to the improvement of medical science.

Today's event is a very precious event where we can exchange experiences of the upgrade of internal medicine cases management by renowned research involving internists, pulmonologists, cardiologists, general practitioners, medical students, nurses, paramedics, and other associated professionals. Now and in the future, Universitas Airlangga will continue to forge very practical cooperative relationships with those parties mentioned before in order to sustain medical expertise and health service in Indonesia.

Last but not least, I greatly hope that all of the honorable guests assembled here will overture your encouragement and generous support for the successful and continued growth of this annual international continuing medical education.

Once again, I am very thankful for your support and participation. Thank you very much.

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ANTI RITUXIMAB ANTIBODY TITER AND THERAPEUTIC RESPONSE IN NON-HODGKIN LYMPHOMA PATIENT RECEIVING R-CHOP TREATMENT

Roethmia Yaniari, Ami Ashariati*, Ugroseno

Department of Internal Medicine, Faculty of Medicine, Dr.Soetomo General Hospital, Universitas Airlangga, Surabaya 60285, Indonesia

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Abstract

Background: *Rituximab as a combination of chemotherapy (R-CHOP) is more effective in the treatment of Lymphoma Non-Hodgkini (NHL). Production of humoral immune response frequently decreases the efficacy of antibody therapy due to premature clearance of antibodies, thus limiting the effectiveness of anti-tumor responses.*

We determined the correlation between anti-rituximab antibody levels and the response of R-CHOP-treated NHL patients who receiving.

Methods: *This study was an observational analytic cross-sectional study on NHL patients in the Division of Hematology of Medical Oncology at Dr.Soetomo General Hospital Surabaya. Anti rituximab antibody titer was measured by ELISA from serum samples and the treatment response was evaluated according to category of response criteria for clinical trial (complete response, partial response, stable disease or progressive disease).*

Results: *This study was enrolled 54 subjects that consisted of 64.8% of male, mean age of patients was 49.167 ± 12,075 years old, stage III was highest (61.6%). Median anti-rituximab antibody titer of 21.55 (9.24 - 197.17) pg/mL. The most progressive disease therapeutic response group was 46.3%. Comparative analysis of anti-rituximab antibody titer in each treatment response group was not significant (p-value = 0.08). The results of the correlation test are significant (p-value = 0.04; r Spearman = -0.27).*

Conclusion: *There was weak negative correlation between anti-rituximab antibody titer and therapeutic response in R-CHOP-treated NHL patients.*

Keywords: *Non-Hodgkin's lymphoma, Anti rituximab antibody, Therapeutic response*

Introduction

Non-Hodgkin's lymphoma (NHL) is a group of heterogeneous malignancies derived from a lymphoid system that generally express B cells and/or T cells and it indicates a disruption in the development of normal precursor stage (1). The addition of rituximab (R) to CHOP regimens has now been widely accepted as a standard regimen for NHL treatment. Another study showed that 6-cycle R-CHOP resulted in CR treatment response of 56% and 58%, respectively (2-4).

In Indonesia, Hodgkin's disease and leukemia, NHL ranks the sixth most common malignancy. The disease has caused a high rate of morbidity and mortality (5). Based on data obtained in the US between 2009 – 2013, there were 19.5 new cases of NHL found every 100.000 people per year, with mortality of 6 per 100.000 people each year (6). NHL can affect the quality of life of its patients, depending on the degree of symptoms severity, support of social environment and other needs (7). The addition of rituximab to standard CHOP regimen will increase the cost of treatment. Therefore, study about the correlation between anti rituximab antibody titer and therapeutic response in NHLpatientswith R-CHOP treatment needs to be conducted.

The CHOP regimen consisting of cyclophosphamide, anthracycline, vincristine and prednisone (9) has been used as the gold standard for aggressive lymphoma therapy for more than 25

Address for Correspondence:
Prof. Ami Ashariati MD., PhD
Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60285, Indonesia
Phone: +6231 5501-1177
E-mail: amiashariati@yahoo.com

years. Patients with aggressive type of NHL are very likely to be cured and CHOP is considered to successfully cure 50% of cases in that population (8). The CHOP regimen. Lymphomas have typical histologic appearances such as immune phenotype with or without CD20 as the surface marker. With the discovery of CD20, the standard of treatment nowadays changes along with the addition of rituximab. Rituximab is one of the examples of the most successful anti-CD20 that has been widely approved to be used as combination of chemotherapy (10). Rituximab is a chimeric monoclonal antibody that is recognized by host's body as a foreign protein, thus stimulating the immune response. As a result, humoral immune response is subsequently generated and encountered Rituximab. (1, 11). Murine-derived rituximab fragments were reported to induce the formation of human anti-chimeric antibody (HACA) in patients receiving rituximab therapy, as in pemphigus patients and other autoimmune diseases such as Systemic lupus erythematosus (12, 13). HACA was also formed in NHL patients receiving rituximab therapy, enabling it to bind to rituximab, disrupt the therapeutic mechanism and reduce the efficacy (14) (10).

According to Association of Indonesia Hematology-Medical Oncology of Internal Medicine guidelines, the therapeutic response to NHL can be evaluated after 4 cycles of chemotherapy, therefore antibody rituximab antibody titer screening will also be performed after the 4th cycle of R-CHOP (5). Based on these considerations, the researchers wanted to analyze the correlation between anti-rituximab antibody titer and therapeutic response in NHL patients who received R-CHOP therapy in Dr.Soetomo General Hospital, Surabaya.

METHODS

This research was an observational research with the cross-sectional study design. The population of the study was NHL patients treated in Dr. Soetomo Surabaya from July 2015 to February 2016. The research samples were patients who meet the inclusion criteria but not the exclusion criteria. NHL patients with either nodal or extranodal who have received 4 cycles of chemotherapy R-CHOP regimen and have never received other chemotherapy regimen or radiotherapy before, willing to participate in research and signed informed consent were categorized as inclusion criteria. While patients with age above 80 years were excluded. The sampling was done by consecutive sampling and interview in IRJ POSA-HOM Outpatient Installation and Medical Inpatient Installation of Dr.Soetomo General Hospital, Surabaya.

Anti-rituximab antibody titer was a parameter that describes the antibody concentration of rituximab in rituximab-treated NHL patients, that was measured using quantitative ELISA from serum samples after 4 cycles of chemotherapy RCHOP regimen, and expressed in pg/mL units. The R-CHOP regimen was a therapeutic regimen in NHL patients, a combination of immunotherapy and chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, administered every 21 days cycle (5, 15).

The instruments used during this research were the ELISA Kit (Sincere Biotech Co., Ltd., Beijing, China) to detect and identify the human anti-rituximab ELISA quantitatively and Ruler or meter with a scale of cm with precision up to 0.1 cm or 1 mm to measure the target lesion, measured at the two longest/bidimensional diameters.

NHL patients, both nodal and extra nodal in IRJ POSA-HOM unit Dr.Soetomo General Hospital that performed anamnesis symptoms related to the disease; examination of the size of the tumor physically and other investigations that meet the inclusion and exclusion criteria which has been given 4 cycles of R-CHOP will be taken serum samples for antiliter titer antibody examination and evaluated the response of therapy based on the measurement of the target lesion physically and the presence or absence of disease-related symptoms , compared with data before chemotherapy, categorized by definition of response criteria for clinical trials including Complete Response, Partial Response, Stable Disease or Progressive Diasease (5, 16). The data obtained then processed statistically.

Data analysis were analyzed using R statistic program, a system for calculation and graph (17). The difference analysis on anti rituximab antibody titer were determined using analysis of variance (ANOVA) test if data were normally distributed. .Kruskal-Wallis would be used if the data were not normally distributed. Spearman correlation test was

used to determine the relationship between titer antibody anti rituximab with therapeutic response .

Results

There were 54 of NHL patients who fulfilled the inclusion criteria, with the proportion of male 35 patients (64.8%) and female by 19 patients (35.2%). The mean age of the patient was 49.167 ± 12.075 years, with the youngest was 16 years old and the oldest was 75 years old. The highest stage was III as much as 33 (61,1%), mostly found severity degree was intermediate grade as much as 33 (61,1%), appearances were diffuse mixed as much as 23 patients (42,6%) (Table 1). We found that the lowest concentration of anti-rituximab antibody titer in 54 LNH patients receiving R-CHOP was 9.24 pg/mL and highest concentration was 197.17 pg/mL, with median antibody concentration of rituximab antibody as much as 21.55 pg/mL.

The responses of therapy were grouped into the progressive disease, stable disease, partial response and complete response, with the mostly found response was progressive disease while least found was stable disease. In this study, the highest distribution of treatment groups was a progressive disease (46.3%), followed by a partial response (31.5%), then the complete response (14.8%) and at least stable disease (7.4%). The subject distribution according to the therapeutic response can be seen in Figure 1.

The statistical test was performed to see the comparison of antibody titer of anti rituximab in each treatment response group by using Kruskal-Wallis test because of abnormal data distribution. The Kruskal-Wallis test of anti rituximab antibody titer in each treatment response group can be seen in

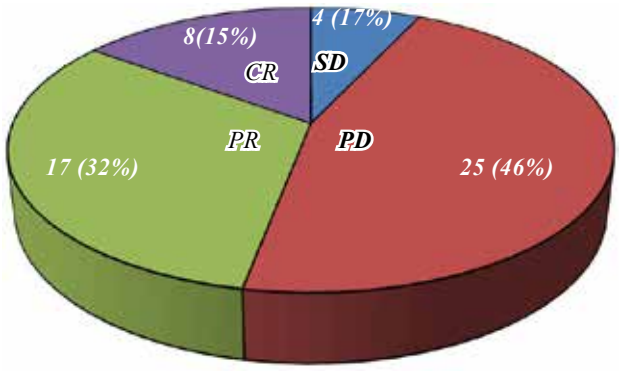

Figure 1. *Distribution of subjects according to therapeutic response*
Notes: *PD – Progressive Disease , PR – Partial Response, SD – Stabile Disease, CR Complete Response*

Table 1

Characteristics of research subjects

Characteristics	Amount (n = 54)	Percentase (%)
Sex		
Male	35	64.8
Female	19	35.2
Age		
≤ 60 year	44	81.5
> 60 year	10	18.5
Stage		
I	4	7.4
II	16	29.6
III	33	61.1
IV	1	1.9
Clinical and histopathologic degree		
Low grade	11	20.4
Small *lymphocytic*	5	9.2
Follicular mixed cell	6	11.1
Intermediate grade	33	61.1
Diffuse mixed	23	42.6
Follicular large cell	1	1.9
Difuse large cell	9	16.7
High grade	10	18.5
Large cell, immune blastic	5	9.2
Lymphoblastic	3	5.6
Small non cleaved cell	2	3.7

Table 2. Kruskal-Wallis test is showed result of p = 0,08, suggesting that there was no significant difference of antibody anti rituximab titer in each group of therapeutic response. The median anti-rituximab antibody titer in the progressive disease group was 22.1 pg/mL; stable disease was 24.735 pg/mL, with the lowest concentration was 22.88 pg/mL and the highest concentration was 52.75 pg/mL. Stable disease was the least found therapeutic response group, which was obtained from 4 of 54 subjects (7.40%). The median anti-rituximab antibody titer in the partial response group was 18.95 pg/mL and at complete response was 16.095 pg/mL. In general, the median reduction of anti rituximab antibodies was accompanied by the increased thera-

Table 2

Comparison of anti rituximab (pg/mL) antibody titer according to treatment response group

Disease	Medium	Min - Max
Progressive Disease (n=25)	22*	10.22-197.17
Stable Disease (n=4)	24.735*	22.88-52.75
Partial Response (n=17)	18.95*	9.24-123.2
Complete Response (n=8)	16.095*	11.95-30.17
* - p = 0.08		

peutic response in NHL patients receiving R-CHOP, although there was a slight increase in titer in the stable disease group. The difference between anti-rituximab antibody titers in each of these treatment response groups can be seen in Figure 2.

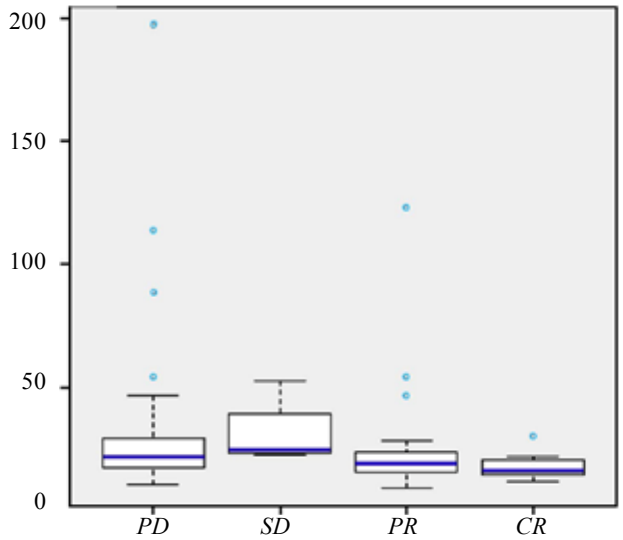

FIGURE 2. *Differences between anti-rituximab antibody titers in each treatment response group*
NOTES: *PD – Progressive Disease , PR – Partial Response, SD – Stabile Disease, CR Complete Response*

Statistically with the unbalanced number and distribution of samples present in each group of therapeutic responses, there was no significant difference in antibody titer of anti rituximab in each treatment response group, but the median trend line antibody titer of rituximab antibody on each - a therapeutic response group showed a antibody titer that decreased along with increasing therapeutic response (Figure. 3).

The result of analysis by using Spearman Rank showed a correlation between anti rituximab antibody titer and therapeutic response in with r value of - 0.27 (-27%) and p-value of 0,04. Spearman's negative r value showed the inverse correlation between anti rituximab antibodies with therapeutic response with r value of 0.27 that was interpreted as a weak correlation strength.

This study showed that there was negative correlation between anti-rituximab antibody titer and the therapeutic response. The therapeutic responses would decrease along with the increase of anti-rituximab antibody titer, vice versa. This correlation can be seen through trend line median antibody titer anti rituximab on the therapeutic response (Figure 3).

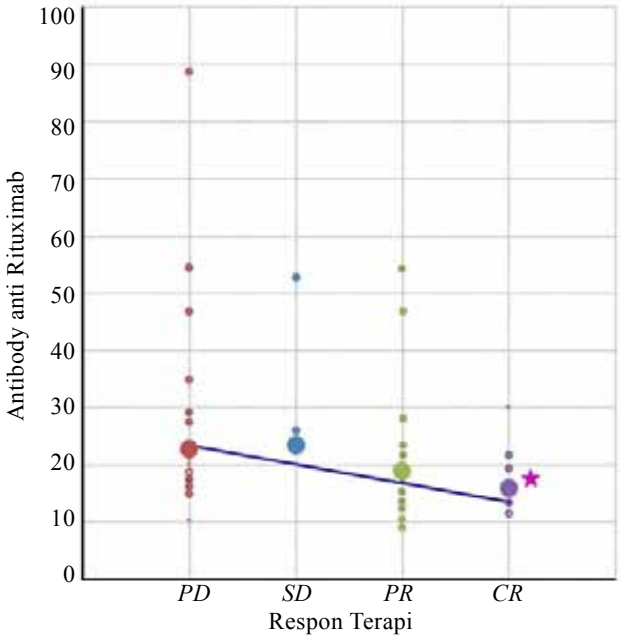

FIGURE 3. *Trend line median antibody titer of anti rituximab in each treatment*
NOTES: *PD – Progressive Disease , PR – Partial Response, SD – Stabile Disease, CR Complete Response, (star)* - Median respon terapi, (stroke) - Linear median respon terapi

DISCUSSION

In this study, from 54 subjects that consisted of 35 male (64%) and 19 female (35.2%), the obtained ratio was 1.85: 1. This was in accordance with research conducted at Dr.Soetomo General Hospital Surabaya, with ratio of 1.5: 1 (21). The risk of NHL appears to increase with the aging process, which mostly occurs in the 60s or so (9). Median age was obtained in almost all NHL subtypes> 50 years, except for high-grade lymphoblastic and small non-cleaved lymphoma, more common in children and young adults. In 37% of patients with low-grade lymphoma were obtained at 35-64 years and only 16% at <35 years of age, but rarely found in children (20).

The subjects of this study had an average age of 49.17 ± 12.075 years, with the youngest age range 16 years and the oldest 68 years, where age group with the highest proportion was age ≤ 60 years as many as 44 out of 54 patients (81.5%), previous research, got age ≤ 60 years counted 29 from 38 patient (76.32%) and got age ≤ 60 years counted 53 from 86 patient (61.63%) (3, 14).

The mostly found initial clinical stages in this study were stage III by 31 patients (57.40%), stage II by 17 patient (31.50%), stage I by 4 patient

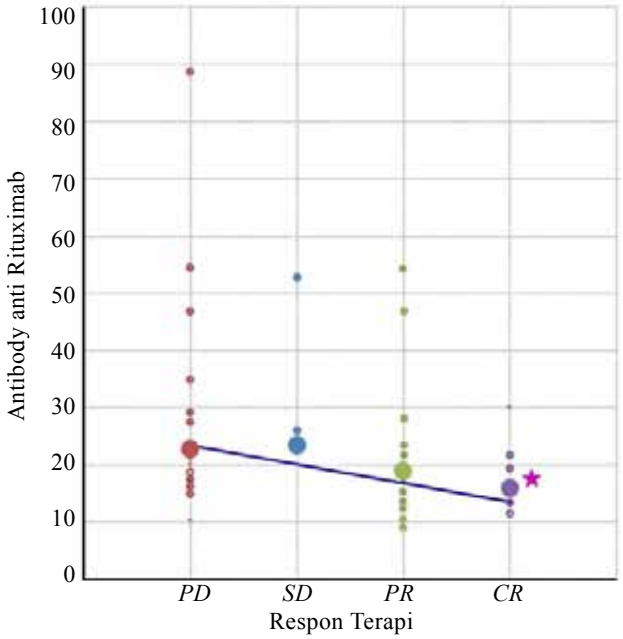

Figure 4. *Trend line median antibody titer of anti rituximab in each treatment*
Notes: *PD – Progressive Disease , PR – Partial Response, SD – Stabile Disease, CR Complete Response, (star)* - Median respon terapi, (stroke) - Linear median respon terapi

(7.4%) and stage IV by 2 patient (3.7%). In contrast to the results of the study comparing two groups of elderly NHL patients who received the R-CHOP and CHOP regimens, in the two groups the highest stage was stage IV (49% vs 49%), stage III (26% vs 24%) , stage II (19% vs. 20%) and at least stage I (6% vs. 7%) (22). This difference was most likely influenced by the use of multimodality that supported a systemic approach in staging.

The severity degree in this study was intermediate grade by 33 patients (61.1%), low grade 11 patients (20.4%) and high grade by 10 patients (18.5%). This was also in line with the data obtained the mostly found severity degree in the US were intermediate grade (41%), low grade (39%) and high grade (20%) (23).

In this study, the most histologic types were diffuse mixed, intermediate grade of 23 patients (42.6%); diffuse large cell, intermediate grade of 9 patients (16.7%); follicular mixed cell, low grade by 6 patients (11.1%); small lymphocytic, low grade of 5 patients (9.2%); large cell, immunoblastic, high grade by 5 patients (9,2%); lymphoblastic, high grade of 3 patients (5.6%); small non cleaved cell, high grade of 2 patients (3.7%) and follicular large cell, intermediate grade of 1 patient (1.9%).

In this study, it was obtained that there was no difference in antibody titer of rituximab antibodies in each treatment response group, although it was generally found the median reduction of anti rituximab antibody titer in line with the improvement of therapeutic response in LNH patients who had received 4 RCHOP cycles. Only in the stable disease response group showed a slight increase in median antibody titer of anti rituximab. This was likely because the number of samples in each of the treatment response groups is unbalanced.

The correlation between anti rituximab antibody with LNH patient therapeutic response which got R-CHOP in this study obtained the result of r value equal to - 0.27 (- 27%) with p-value equal to 0.04 less than 0.05 (α = 5%), meaning correlation between anti-rituximab antibody titers with therapeutic response in LNH patients receiving R-CHOP in Dr.Soetomo General Hospital, Surabaya was weak. Negative or opposite direction of correlation means the decrease of the therapeutic response, the antibody titer of anti rituximab will be higher.

Conclusion

There was weak negative correlation between anti-rituximab antibody titer and the therapeutic response. The therapeutic responses would decrease along with the increase of anti-rituximab antibody titer, vice versa.

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