ejpmr, 2022,9(6), 97-104

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

RESPONSE TO RITUXIMAB IN NON-HODGKIN LYMPHOMA PATIENTS AT NATIONAL ONCOLOGY CENTER, ADEN, YEMEN, 2017-2020: RETROSPECTIVE COHORT STUDY

Magdi Saif Aldaeri[1*], Gamal Abdul Hamid[2], Mohammed A. Al Amad[3] and Yasser Ghaleb[4]

[1]MSc Ministry of Public Health and Population, Yemen Field Epidemiology Training Program, Sana'a, Yemen.
[2]PhD, Professor of Hematology-Oncology, Aden university/G. Director, National Program of Cancer Control / Chairman of WAMS, World Academy of Med, Science, Yemen.
[3]MPH, Ministry of Public Health and Population, Yemen Field Epidemiology Training Program, Sana'a, Yemen.
[4]MSc, Ministry of Public Health and Population, Yemen Field Epidemiology Training Program, Sana'a, Yemen.

***Corresponding Author: Magdi Saif Aldaeri**

MSc Ministry of Public Health and Population, Yemen Field Epidemiology Training Program, Sana'a, Yemen.

Article Received on 12/04/2022 **Article Revised on 01/05/2022** **Article Accepted on 22/05/2022**

ABSTRACT

Background: The study aimed to determine the long-term response of rituximab on Non-Hodgkin Lymphomas (NHL) patients. **Methods:** A retrospective cohort study was conducted in the National Oncology Center in Aden by review of medical registries for NHL patients from 2017-2020. SPSS version 23 was used for the analysis of data, and Kaplan Meier survival curve was used to measure overall survival (OS) and progression-free survival (PFS) between two groups CHOP and R-CHOP in two follow up periods (12-months and 4-years). Cox regression was used to evaluate the association between the risk factors. **Results:** Of 100 patients, 50 for each group of CHOP and R-CHOP. < 60 years represented 70%. Advanced Stage represented 64% and DLBCL represented 47% of all subtypes of NHL. Significant association difference in OS in two periods of follow-up (12-month and 4-years) for CHOP vs. R-CHOP was 63% vs. 86%, and 10% vs. 33%, respectively (*P=0.01 and P=0.04*). In contrast, the difference was non-statically significant in the PFS in two periods 39% vs. 66%, and 12% vs. 27% for CHOP vs. R-CHOP, respectively (*P=0.10 and P=0.31*). The age group > 60 years, ≥ 6 cycles of chemotherapy received, abnormality of LDH, and married patients were the significantly hazard proportion ($P < 0.05$). **Conclusion**: The addition of rituximab to CHOP had a statistical difference in OS and there is no difference in PFS. Elderly, married patients, > 6 cycles of chemotherapy received, and abnormality LDH were poor prognostic factors. Providing oncology center with rituximab for ongoing use it of NHL patients are recommended.

KEYWORDS: Non-Hodgkin lymphoma, CHOP, rituximab, Survival, Yemen.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is an aggressive chronic lymphoproliferative disorder of the immune system that comprises many subtypes, each with distinct epidemiology, etiology, histology, immunophenotypic, genetic, clinical features; and responses to therapy, which can make diagnosis difficult. B-cell NHLs represented almost all of the cases 85%, while T/Natural killer cells represented 15%.[1]

Anaplastic large cell, follicular, B cell lymphoma, diffuse large cell, lymphoblastic, mantle cell, mycosis fungoides, primary CNS lymphoma, and cutaneous T-cell lymphoma are the subtypes of NHL. Furthermore, it may result from chromosomal translocations, infections, environmental factors, immunodeficiency states, and chronic inflammation.[2]

In 1982, the NHL was classified by morphology and clinical behavior (i.e., low, intermediate, or high grade). Then in1990s, the Revised European-American Lymphoma (REAL) classification attempted to apply immunophenotypic and genetic features in identifying distinct clinicopathologic NHL entities.[3] The World Health Organization (WHO) classification divided NHL into those of B-cell origin and those of T-cell and natural killer (NK)–cell origin according to the REAL approach.[4]

The treatment of non-Hodgkin lymphoma (NHL) varies greatly, depending on many factors: Tumor stage, Phenotype (B-cell, T-cell or Natural Killer cell/null-cell), Histology (i.e., low, intermediate, or high grade), Symptoms, Performance status, Patient age, Comorbidities.[5]

Rituximab is a monoclonal antibody that targets the CD20 antigen, which is expressed on the surface of pre-B and mature B-lymphocytes. Rituximab binds to CD20 after mediates B-cell lysis (or breakdown). The possible

mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.[6]

NHL is the most prevalent hematopoietic neoplasm, representing approximately 4.3% of all cancer diagnoses and ranking seventh in frequency among all cancers. The incidence of NHL has increased 168% since 1975 (while survival has improved by 158%).[7]

Globally, the latest GLOBOCAN data in 2018 estimated 509,600 new cases of NHL were diagnosed; comprising 2.8% of worldwide cancer diagnoses and the age-standardized risk of NHL was 6.7 among men and 4.7 among women. In addition, an estimated 248,700 deaths were attributable to NHL, and the NHL's 5-year survival from 2010 to 2016 in the US was 72.7%.[7]

In the Eastern Mediterranean region EMRO, 2020, according to GLOBOCAN, the NHL represented as the eighth rank of all cancer in the region, incidence rate of 4.2%, and case mortality rate of 3.4%, the prevalence of 5-years 10.68/100,000 of the population.[8]

In Yemen, Non-Hodgkin Lymphoma was a major health problem that represents the second most common type of cancer (10.1%) in males, and the third common type in females (6.6%) in 2011.[9] In Aden governorate, the NHL represented the first common hematological malignancy in 2010.[10] In 2013, Lymphoma represented 9.8% of all cancer patients who attended the national oncology center, and the NHL represented 65% of all lymphomas patients.[11]

Rituximab entered into the protocol of NHL in NOC, although of its higher cost, there is no previous study published in Yemen and neighboring countries to measure the impact and response of it on lymphomas patients. The present study aims to determine the long-term response of rituximab on NHL patients and measure the survival rate among patients when treated with R-CHOP or CHOP.

METHODS

Study design

A retrospective cohort study was conducted during the period of (2017-2020).

Study area and Setting

The study was conducted in the National Oncology Center (NOC), Aden governorate. NOC was established in 2013 at Alsadaqa hospital. The majority of attendees to the center are from Aden governorate and many neighboring Governorates such as Lahj, Abian, Aldhale, Shabowh, and other governorates. The number of tumor cases until October 2021 reached 8960 cases for the center, where the number of males reached 3157 cases, females 4303, and children 1550, with an increase of cases in the last years. In addition, the center receives approximately 1200 cases annually.

Study Population

All the Non-Hodgkin lymphoma patients that registered in NOC from 2017-2020 and received at least four cycles of R-CHOP& CHOP protocol were included in this study.

Definitions and selection criteria

Exposed cases were defined as all lymphoma patients > 16 years in NOC received at least four cycles of R-CHOP protocol[1] and lymphoma patients > 16 years in NOC received at least four cycles of CHOP protocol were defined as non-exposed.

Inclusion criteria

Patients with NHL received at least four cycles of R-CHOP protocol or CHOP, the age more than 16 years and diagnosed between 2017-2020 years.

Exclusion criteria

The patient received less than four cycles of chemotherapy (R-CHOP and CHOP) or received other protocols than R-CHOP or CHOP protocol or both protocols of R-CHOP and CHOP. In addition, patients with age less than 16 years or diagnosed before 2017 and after 2020.

Data collection tools and procedures

We reviewed patients' registries and files in NOC by a trained team (principal investigator & data collectors). Abstracting form used to collect all variables of the patient files regarding patients' demographics (e.g., sex, age, job, place of birth, marital status) and clinical features such as stage of disease, a subtype of NHL, B symptoms, and outcomes. In addition, the abstracting form included data about date of diagnosis, start chemotherapy, follow up, lack of follow up, death, negative scan, and relapse for each patient as well as laboratory investigations.

Quality assurance and control

The principal investigator monitored all the processes of data collection from patient registries and each sample of the abstracting forms was evaluated to be sure that collection is done perfectly as instructed in training. Data collected from all collectors and frequencies were used to check data before data entry.

Data entry and management

Data entered in the excel format of the abstracting form and exported into SPSS version 23 for analysis. Univariate and multivariate cox regression analysis was conducted with the final model. Secondary clinical indicators assessed at the end of chemotherapy protocols were overall survival (OS) is the percentage age of people who can still live for a definite time after they were clinically diagnosed with a certain disease like cancer or started therapy for that disease. Progression-free survival (PFS), The PFS is the period during treatment and after the management of a malignant disease like cancer, patient lives with the disease but it

does not get worse. That measured from date of diagnosis to date of relapse or progression of the lesion or death.

Kaplan Meier survival curve analyses were employed to measure OS and PFS for the two groups of cases (CHOP/ R-CHOP) to find any difference in response due to treatment protocols. A P-value of less than 0.05 at a confidence interval of 95% is considered statistically significant.

RESULTS

Descriptive analysis

A total of 200 cases of NHL were admitted at NOC-Aden in the last four years, 100 cases of them were well-matched to inclusion and exclusion criteria of this study, of whom 50 cases were treated according to CHOP and 50 cases with R-CHOP. The overall mean age of patients was 48.8 years (± 16). Table 1 shows the characteristics of NHL patients, aged less than 60 years, male, non-employed, and Married patients formed the majority of cases, 70%, 57%, 61%and 81%, respectively. 25 % of cases were diagnosed in 2017.

Pathological characteristics of NHL, Ann-Arbor advance stage Ⅲ, Ⅳ represented 64, and with an absence of B-symptoms (fever, drenching night sweats, and loss of more than 10 percent of body weight over 6 months) in 67% of cases. Nodal lesion represented 54% and diffuse large B cell lymphoma (DLBCL) represent 47% of all NHL subtypes, (66% in R-CHOP group).

The abnormality of laboratory investigations of LDH 62%, B2M 61%, while normality of WBC 84% and bone marrow 95%. Positive cases for CD20 represent 67%.

Advanced stages of disease and mortality were found to be significantly associated with patients who were treated with CHOP. (*p=0.03 and p =0.02*), respectively.

Table 1: Characteristics of Non-Hodgkin lymphoma patients related to protocol, NOC-Aden, Yemen 2017-2020.

Variables	Total n= 100		CHOP n=50		R-CHOP n=50		P-Value
	Frequency	Percent	Frequency	Percent	Frequency	Percent	
Age							
≤60	70(70)		34(49)		36(51)		0.82
>60	30(30)		16(53)		14(47)		
sex							
Male	57(57)		29(51)		28(49)		1.000
Female	43(43)		21(49)		22(51)		
Job							
Employed	39(39)		19(49)		20(51)		0.8
Not- Employed	61(61)		31(51)		30(49)		
Marital state							
Single	19(19)		12(63)		7(37)		0.2
Married	81(81)		38(47)		43(53)		
LDH							
Normal	38(38)		21(55)		17(45)		0.40
Abnormal	62(62)		29(47)		33(53)		
B2M							
Normal	39(39)		24(62)		15(38)		0.06
Abnormal	61(61)		26(43)		35(57)		
WBC							
Normal	84(84)		44(52)		40(48)		0.27
Abnormal	16(16)		6(38)		10(62)		
CD20							
Positive	67(67)		17(25)		50(75)		N/A
Negative	33(33)		33(100)		0		
Bone marrow							
Normal	95(95)		49(52)		46(48)		0.16
Infiltrated	5 (5)		1(20)		4(80)		
Diagnosed years	27(27)		15(56)		12(44)		
2017	26(26)		20(77)		6(23)		
2018	21(21)		9(43)		12(57)		0.0012
2019	26(26)		6(23)		20(77)		
2020							
Sub-type of NHL							
DLBCL	47(47)		16(34)		31(66)		0.0181
Unclassified B-cell	29(29)		20(69)		9(31)		

Follicular	13(13)	5(38)	8(62)	
Other B-cell	4(4)	2(50)	2(50)	
T-cell	5(5)	5(100)	0	
NK cell	2(2)	2(100)	0	
B-Symptoms				
Present	33(33)	14(42)	19(58)	0.28
Absent	67(67)	36(54)	31(46)	
Stages of NHL				
I - II	36(36)	23(64)	13(36)	**0.03**
III-IV	64(64)	27(42)	37(58)	
Lesion site				
Nodal	54(54)	29(54)	25(46)	0.54
Extra-nodal	46(46)	21(46)	25(54)	
Chemotherapy Cycle				
<6	35(35)	21(60)	14(40)	0.21
≥6	65(65)	29(45)	36(55)	
Outcome				
Alive	80(80)	35(44)	45(56)	**0.02**
Died	20(20)	15(75)	5(25)	

Survival analysis

Two periods to follow up with the patients in our study were determined. First, the patients of NHL during four years were followed up every 12 months; from the date of diagnosis to the end period for each group (CHOP & R-CHOP). The overall survival (OS) for 12-month for CHOP and R-CHOP was 63% and 86%, respectively with a p-value of (*P*=0.01). While the progression-free survival (PFS) for the same period was 39% and 66% for CHOP and R-CHOP respectively with a p-value (*P*= 0.10) (Figure 1).

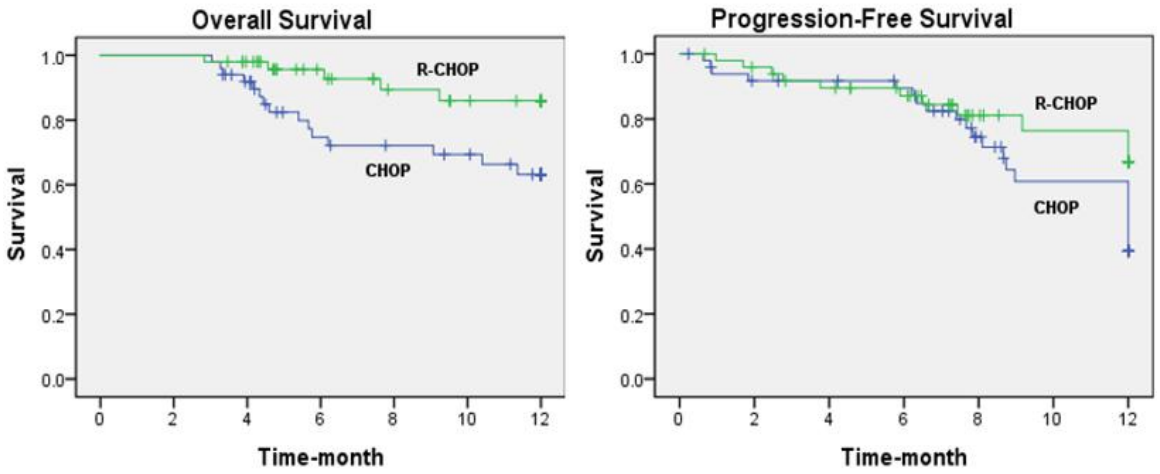

Figure 1: Kaplan Meier survival for overall survival and progression free survival in 12-month followup

Second, the patients were followed up for four years, the overall survival (OS) for CHOP and R-CHOP was with little difference 10% and 33%, respectively with P-value (*P*=0.04). While progression-free survival (PFS) during four years follow-up was 12% and 27% for CHOP and R-CHOP respectively with P-value (*P*= 0.31) (Figure 2).

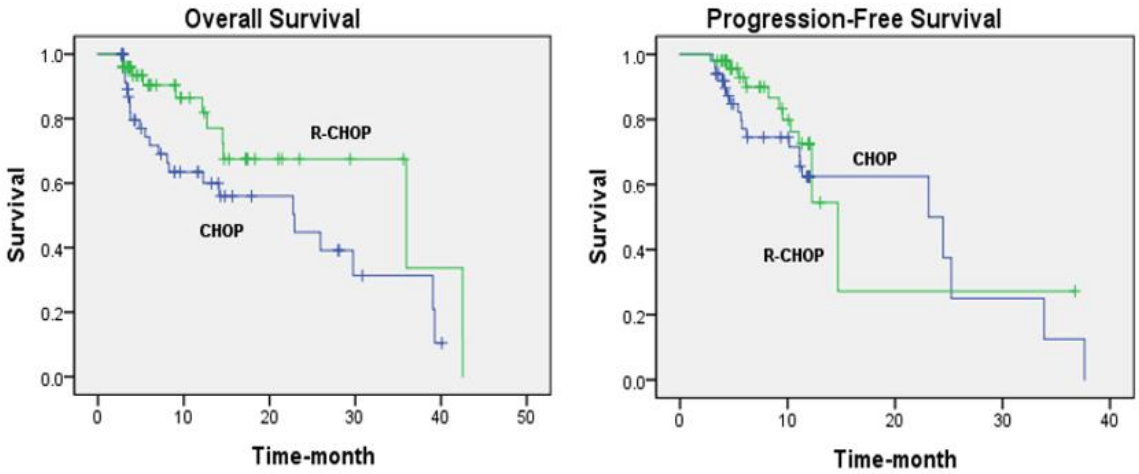

Figure 2: Kaplan Meier survival for overall survival and progression free survival in 4-Years followup

Table 2 illustrates the hazard proportion in many characteristics of patients by using cox regression. The age group more than 60 years, more than 6 cycles of chemotherapy, abnormality of LDH, and married patients were the significantly hazard proportion that was associated with poor prognostic factors with P-value of 0.009, 0.001,0.010, and 0.011, respectively.

Table 2: Cox proportion hazard of Non-Hodgkin lymphoma cases, NOC-Aden, Yemen

Variables	Hazard Ratio	95% C.I.	P-Value
Treatment protocol (CHOP & R-CHOP)	2.554	0.914 - 7.133	0.0736
Age group (≤60 &>60)	2.927	1.132 - 7.566	**0.009**
B-symptoms (Yes & No)	1.804	0.814 - 3.995	0.1461
B2M (Normal & Abnormal)	1.244	0.550 - 2.814	0.6009
Bone marrow (Normal & Infiltrated)	0.000	NA	NA
CD20 (Positive & Negative)	1.363	0.452 - 4.109	0.5822
Chemotherapy cycle (<6 & ≥6)	0.040	0.012 - 0.131	**0.000**
LDH (Normal & Abnormal)	3.508	1.342 - 9.166	**0.0105**
Marital state (Single & married)	4.973	1.438 - 17.194	**0.0113**
Sex (Male & Female)	0.467	0.183 - 1.193	0.1115
Stage of NHL (I- II & III, IV)	0.988	0.423 - 2.307	0.9779
WBC (Normal & Abnormal)	0.585	0.141 - 2.421	0.4591

DISCUSSION

The burden of the NHL has increased distinctly in the last years in Yemen. In patients with NHL, the addition of rituximab to standard treatment significantly enhanced response to therapy and overall outcomes. Rituximab is currently approved for the treatment of relapsed and refractory indolent lymphomas as single-agent therapy and as initial therapy in combination with standard chemotherapy regimens.[12]

NHL is most often diagnosed in an elderly patient that is aged >60 years, but there is an exception for some types of NHL that are diagnosed in an adult patient.[13] Our study showed the mean age of the patient was 48 years, which is similar to the previous study conducted in Aden, Hadramoot governorates[10, 14], and other studies in China and Mexico.[1, 15] This is due to our patients being contained in all subtypes of NHL.

Regarding gender, our study showed no great difference between males and females (57%). This result is consistent with previous studies in Southeastern governorates of Yemen, Saudia Arabia, and Mexico.[1, 16-18] In contrast, studies conducted in Yemen, and among Chinese patients showed that females more than males,[14, 15] this attributed to the male developing disease more likely than females.[19]

Regarding pathological characteristics, advanced stages (III, IV) represented the majority of cases; these findings were in agreement with studies reported in Saudia Arabia, Mexico, and France.[1, 18, 20, 21] On other hand, a study in China revealed that most cases were in stages I, II.[15] This difference may be due to the lack of early screening of disease in our country.

About 30-40% of NHL patients complain of B-symptoms at the time of diagnosis.[5] Our finding revealed that two-thirds of patients did not complain of

B-symptoms (67%), which is nearly similar to studies conducted in Mexico and Korea that were (65%, 68%) respectively, and higher than reported from Saudia Arabia (52%).[1, 18, 22]

Cervical lesions represent 28% of all cases in the first of other lesion sites, agrees with a study conducted in Hadramoot[14], and different with a study conducted in Aden which revealed the common lesion was in the abdomen.[17]

Diffuse large B cell lymphoma was the most frequent subtype of NHL in our study; this result is similar to a study conducted in Hadramoot Yemen, Aseer Saudia Arabia, and a previous study Middle East region.[14, 18, 23] This is due to DLBCL being the most common form of lymphoma that represents about 30% of NHL.[24]

Regarding laboratory investigations, our study showed the abnormality of LDH and B2M in most cases, this finding was agreed with a study conducted in Korea[22], and disagreed with the findings of a study conducted in China.[15] In addition, most cases were a normal count of WBC; a similar result was reported in Saudia Arabia.[18] and CD20 was positive in 67% of patients in our study, which is lower than findings from Saudia Arabia 82%.[18] This difference may be due to variances in sample size, and the percentage of B cell lymphoma that contains about 98% of positive CD20. Furthermore, Only 5% of cases had bone marrow infiltration, which is consistent with findings reported in a previous study.[22]

The incidence rate of new cases of non-Hodgkin lymphoma was 19.6 /100,000 per year and the death rate was 5.3 /100,000 per year globally, furthermore, the mortality was about fourth of diagnosed cases of NHL.[25] Our study found that the overall fatality rate was 20% and 30% & 10% for CHOP and R-CHOP, respectively, which is close to the global rate. This result is slightly lower than a study conducted in Korea that found the overall fatality rate was 31% and 57%& 14% for each group, and another study in France showed 35% and (41% & 29%).[20, 22]

In this study, the survival outcome of two groups (CHOP& R-CHOP) was estimated in two follow-up periods in 12 months and 4-year, according to previously evaluated cancer survival analysis.[26] Our findings revealed that the overall survival (OS) in 12-month was 63% and 86%, for CHOP and R-CHOP respectively. This was nearly similar to a study conducted in China for the same period 12-month (75%& 93.8%).[27] In addition, the progression-free period (PFP) in our study was 39% and 66% for CHOP and R-CHOP, respectively, lower than studies conducted in China (52.8%& 81.2%).[27] This could be due to many causes such as the low quality of medical services in Yemen compared with other countries, decrease patient outcomes that lead to poor regular follow-up, and most patients coming in advanced stages.

The survival rate has been improving since 1997, thanks to treatment advances. From 2009 to 2018, the death rate decreased by 2% annually. The overall 5-year survival rate for people with NHL is 73%.[28] The 4-years survival rate for patients in our study was 10% and 33% for overall survival of CHOP and R-CHOP groups, respectively. This result was much lower than 5-years survival in the United States (73%), a study conducted in Mexico (61.8% & 65%), and in Korea (94.7% &84.7%).[1,28, 29] on the other hand, the progression-free survival (PFS) was 12% and 27% for CHOP and R-CHOP, respectively. This is also much lower than other studies conducted in Mexico (63.8 and 51.2%), Korea (50.0% vs. 79.0%), and Germany (59% & 79%).[1,22, 30]

Our finding revealed significant overall survival (OS) of two groups and not significant progression-free survival (PFS), this was consistent with the previous study conducted in China and France that found significant overall survival.[15, 20] In contrast, previous studies conducted in Korea found significant progression-free survival and not significant overall survival, and another study conducted in Mexico found no significance for both overall and progression-free survival.[1, 22] This difference may be due to the most patients were in advanced stages.

The prognosis for non-Hodgkin lymphoma (NHL) varies with the histology, the stage of disease at diagnosis, and the response of the disease to therapy. Furthermore, age ≥60 years, elevated lactate dehydrogenase (LDH) level, Stage III or IV disease, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, and two or more extra-nodal sites.[13] In our study, the significant prognostic factors were the age > 60 years, >6 cycles chemotherapy, abnormality of LDH, and married patient with P-value <0.05. This conforms to studies conducted in Korea and China that found age > 60 years were poor prognostic factors.[15, 22] In contrast, many studies conducted in different countries found these factors not significantly associated with protocol treatment.[1,20,29] The main limitation in our study was the poor documentation for some processes of treatment of patients and the follow-up results. Lack of a computerized system in the treatment center leads to a lack of the outcome of many patients.

In conclusion, the addition of rituximab to CHOP chemotherapy had a statistical difference in overall survival and there is no difference in PFS. Elderly, married patients, more than 6 cycles of chemotherapy received, and abnormality of LDH were the most important prognostic factors. Therefore, providing the oncology center with Rituximab for ongoing use of NHL patients especially those under 60 years, further assessment for hospital-related risk factors that lead to decreased survival are recommended.

ACKNOWLEDGMENTS

The authors would like to acknowledge the Training Programs in Epidemiology & Public Health Interventions Network (TEPHINET) and Yemen Field Epidemiology Training Program for their technical support. In addition, the National Oncology Center, Aden facilitate all process of data collection.

REFERENCES

1. Jaime-Pérez JC, Gamboa-Alonso CM, Vázquez-Mellado de Larracoechea A, Rodríguez-Martínez M, Gutiérrez-Aguirre CH, Marfil-Rivera LJ, et al. Non-Hodgkin lymphomas: impact of rituximab on overall survival of patients with diffuse large B-cell and follicular lymphoma. Archives of medical research, 2015; 46(6): 454-61.
2. Armitage JO, Gascoyne RD, Lunning MA, Cavalli F. Non-hodgkin lymphoma. The Lancet, 2017; 390(10091): 298-310.
3. Singh R, Shaik S, Negi BS, Rajguru JP, Patil PB, Parihar AS, et al. Non-Hodgkin's lymphoma: A review. Journal of Family Medicine and Primary Care, 2020; 9(4): 1834.
4. Hennessy BT, Hanrahan EO, Daly PA. Non-Hodgkin lymphoma: an update. The lancet oncology, 2004; 5(6): 341-53.
5. Sanjay Vinjamaram M, MPH; Chief Editor: Emmanuel C Besa, MD. Non-Hodgkin Lymphoma (NHL) Feb 25, 2021. Available from: https://emedicine.medscape.com/article/203399-overview#showall.
6. DrugBank. Rituximab 2021. Available from: https://go.drugbank.com/drugs/DB00073.
7. Thandra KC, Barsouk A, Saginala K, Padala SA, Barsouk A, Rawla P. Epidemiology of Non-Hodgkin's Lymphoma. Medical Sciences, 2021; 9(1): 5.
8. WHO. Global Cancer Observation 2020 [updated 11/7/2021]. Available from: https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=cancer&mode_population=continents&population=900&populations=900_993&key=asr&sex=0&cancer=39&type=2&statistic=5&prevalence=1&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&include_nmsc=1&include_nmsc_other=1#collapse-group-1-2-3.
9. Bawazir AA. Cancer incidence in Yemen from 1997 to 2011: a report from the Aden cancer registry. BMC Cancer, 2018; 18(1): 540.
10. Hamid GA. The Pattern of Hematological Malignancies at Al-Gamhouria Teaching Hospital, Aden, Yemen, from 2008 to 2010. Turkish Journal of Haematology, 2012; 29(4): 342.
11. Eman Abdullah Larde, Ashwal AAA. Lymphomas Cancer Registry Data Analysis Report, National Oncology Center 2012-2013 2013 [cited 2021]. Available from: http://www.yfetp.com/.
12. Dotan E, Aggarwal C, Smith MR. Impact of Rituximab (Rituxan) on the Treatment of B-Cell Non-Hodgkin's Lymphoma. P & T : a peer-reviewed journal for formulary management, 2010; 35(3): 148-57.
13. Mohammad Muhsin Chisti M, FACP; Chief Editor: Emmanuel C Besa, MD. B-Cell Lymphoma Apr 27, 2021. Available from: https://emedicine.medscape.com/article/202677-overview#a6.
14. Humam M, Al-Nakhbi N, Melkat A, Almontaser T, Binnabhan A. Malignant lymphoma in Hadhramout Sector, Yemen: a retrospective study of 170 cases classified according to the WHO classification. Journal of Current Medical Research and Practice, 2016; 1(2): 6-11.
15. Huang Y, Ye S, Cao Y, Li Z, Huang J, Huang H, et al. Outcome of R-CHOP or CHOP regimen for germinal center and nongerminal center subtypes of diffuse large B-cell lymphoma of Chinese patients. TheScientificWorldJournal, 2012; 2012: 897178.
16. Abdul Hamid G. MALIGNANT LYMPHOMA IN SOUTHEASTERN of YEMEN. TJH, 2000; 18.
17. BALQIS AL-SAYEED ABDULLA EBRAHIM MD, AHMED SALEH OMER AL-GEFRI, M.D., NASSER ALBISHI MD, AHMED MUTHANNA. Patterns of Malignant Lymphoma among Admitted Patients inAl Gamhoria Hospital, Aden, Yemen. The Medical Journal of Cairo University, 2021; 89(March): 175-9.
18. Alyahya N, Adiga B, Alwadei A, Alshahrani G, Alyahya F. The clinico-pathological profile of non-Hodgkin's lymphoma in Aseer region of Saudi Arabia. BMC Research Notes, 2019; 12(1): 418.
19. Cancer.Net. Lymphoma - Non-Hodgkin: Risk Factors 2021. Available from: https://www.cancer.net/cancer-types/lymphoma-non-hodgkin/risk-factors.
20. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. The New England journal of medicine, 2002; 346(4): 235-42.
21. Rauf MS, Akhtar S, Maghfoor I. Changing trends of adult lymphoma in the Kingdom of Saudi Arabia - comparison of data sources. Asian Pacific journal of cancer prevention: APJCP, 2015; 16(5): 2069-72.
22. Ahn HK, Kim SJ, Yun J, Yi JH, Kim JH, Won YW, et al. Improved treatment outcome of primary mediastinal large B-cell lymphoma after introduction of rituximab in Korean patients. International journal of hematology, 2010; 91(3): 456-63.
23. Yaqo RT, Jalal SD, Ghafour KJ, Hassan HA, Hughson MD. Non-Hodgkin Lymphoma in the Middle East Is Characterized by Low Incidence Rates With Advancing Age. Journal of Global Oncology, 2019; 5: 1-10.
24. Cancer.Net. Lymphoma - Non-Hodgkin: Subtypes 2021. Available from:

https://www.cancer.net/cancer-types/lymphoma-non-hodgkin/subtypes.
25. INSTITUTE NC. Cancer Stat Facts: Non-Hodgkin Lymphoma 2021. Available from: https://seer.cancer.gov/statfacts/html/nhl.html.
26. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Controlled clinical trials, 1996; 17(4): 343-6.
27. Wu HJ, Zhang QY, Chen DF, Guan XJ, Zhang BL, Ma J. [Comparison of rituximab plus CHOP regimen and CHOP regimen alone for treatment of newly diagnosed patients with diffuse large B-cell lymphoma]. Ai zheng = Aizheng = Chinese journal of cancer, 2005; 24(12): 1498-502.
28. Board CNE. Lymphoma - Non-Hodgkin: Statistics 2021. Available from: https://www.cancer.net/cancer-types/lymphoma-non-hodgkin/statistics.
29. Sohn BS, Kim SM, Yoon DH, Kim S, Lee DH, Kim JH, et al. The comparison between CHOP and R-CHOP in primary gastric diffuse large B cell lymphoma. Annals of hematology, 2012; 91(11): 1731-9.
30. Pfreundschuh M, Trümper L, Osterborg A, Pettengell R, Trneny M, Imrie K, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. The Lancet Oncology, 2006; 7(5): 379-91.