Original Research

CLINICAL AND PROGNOSTIC FEATURES OF NON HODGKIN LYMPHOMA AND PRELIMINARY EFFECTIVE EVALUATION OF R-CHOP REGIMEN IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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ABSTRACT

Background: WHO 2008 classification of Non Hodgkin Lymphoma (NHL) has been introduced and got consensus internationally. However, studies on NHL according to WHO 2008 classification are limited in Vietnam. In terms of treatment, the R-CHOP regimen is still the most commonly used regimen for the treatment of moderate or high grade malignant lymphoma tumors. However, its effectiveness on each type has not been specifically studied. Purpose of this research is to evaluate of clinical and subclinical characteristics of NHL patients according to the 2008 WHO classification on lymphoid neoplasms and to evaluate preliminary effective of diffuse large B cell lymphoma (DLBCL) patients with R-CHOP regimen.

Materials and methods: A prospective descriptive study was conducted on 48 patients diagnosed with NHL undergoing treatment at the Hue University Hospital from July 2019 and Hue Central Hospital from April 2020 to present.

Results: The mean age was 52.4 years, male/female ratio = 1.3/1, the most common primary tumor site was lymph nodes with 54.3%. Stage IV was found in 37.5% of all cases. DLBCL was the most common type, accounted for 58.3%, whereas marginal zone lymphoma had the lowest incidence (2.1%). According to the International Prognostic Index (IPI), low risk, low-intermediate risk, high-intermediate risk, high risk group were 43.6%; 25.0%; 18.8%; 12.6% respectively. 34.8% patients responsed completely after 3 cycles and after 6 – 8 cycles, 58.8% patients achieved complete response. Grade III, IV neutropenia, grade I, II peripheral neuropathy and grade I, II thrompocytopenia were the most common side effect observed.

Conclusions: DLBCL is the most common Non Hodgkin Lymphoma. R-CHOP regimen has a good response after 6-8 cycles in DLBCL diseases and is well tolerated that the adverse events are mostly able to control effectively.

Keywords: Non Hodgkin Lymphoma; diffuse large B-cell, R-CHOP regimen, Hue.

I. INTRODUCTION

Accoding to estimates from the Globocan 2018, there were 509.590 patients diagnosed with Non Hodgkin Lymphoma (NHL) worldwide with 248.724 cancer deaths per year [1]. NHL derived primarily from the lymph nodes. Since lymphocytes spread throughout the body, lymphoma could also arise in nodal and extranodal sites. Therefore, the clinical and paraclinical features are very diverse. Improved diagnostic accuracy and classification are becoming increasingly indispensable, contributing to the treatment and prognosis of NHL. The classification system are in a continuous evolution from the 20th century. In the last two decades, with increasing knowledge of the immune system and related gene abnormalities, the classification of NHL has changed significantly. From the original classification of Gall and Mallory, Rappaport's classification, then Kiel's classification, WF's practical formula classification were used. However, these classifications are still limited when applied clinically. Since the 1990s, a new proposal of the International Lymphoma Study Group (ILSG), combining several features of Kiel and practical formula classification, has been presented and has been widely used. Until 2001, the first WHO classification has been introduced (with the 2008 revision), being the first international consensus classification, which considers not only morphological observation but also immunological and genetic finding. Therefore, it helped to better understand etiology, pathogenesis, clinical manifestations, treatments and prognosis [2]. For more than two decades, the CHOP regimen including cyclophosphamide, doxorubicin, vincristine and prednisolone has been considered the gold standard approach in the treatment of most DLBCL [3]. A number of later studies have demonstrated that adding rituximab (the anti-CD20 monoclonal antibody) to CHOP regimens has significantly improved the complete response rate, reduced recurrence rates and improved EFS,

OS in patients with DLBCL [3]. In other B-cell malignant lymphomas, the R-CHOP regimen has also been given to patients with moderate or high malignancies. However, recent studies have shown that a number of molecular subtypes of DLBCL have different responses to the R-CHOP regimen [4]. In terms of prognosis, the International Prognostic Index (IPI) is now used for almost all sybtypes of NHL and is effective in terms of prognosis and treatment orientation [5, 6]. In Vietnam, with the application of immunohistochemistry techniques, the classification of NHL types is becoming more and more accurate. However, studies on NHL according to WHO 2008 classification are limited. There has been a study on the epidemiology of this disease according to WHO classification by Vu Duc Binh at the National Institue of Hematology and Blood Transfusion [7]. In Hue, there have been a number of studies on NHL related to epidemiology according to Rye 1966 classification, practical formula and cell line classification [8, 9]. In terms of treatment, the R-CHOP regimen is still the most commonly used regimen for the treatment of moderate or high grade malignant lymphoma tumors [7]. However, its effectiveness on each type has not been specifically studied.

Therefore, we conducted a clinical and prognostic description of NHL and preliminary effective evaluation of R CHOP regimen in patients with DLBCL with the following goals:

1. To evaluate of clinical and subclinical characteristics of NHL patients

2. To evaluate preliminary effective of DLBCL patients with R CHOP regimen.

II. PATIENTS AND METHODS
2.1. Patients

There were 48 patients diagnosed with NHL undergoing treatment at the Hue University Hospital from July 2019 and Hue Central Hospital from April 2020 to present. Patients were diagnosed

NHL according to the WHO 2008 classification by using histology and immunohistochemistry. The patients agreed to participate in this study and have sufficient medical record documentation

2.2. Methods

2.2.1. Research methods: Prospective descriptive study

2.2.2. Assessment and analysis

Patients' general characteristics: age, gender, hepatitis B, site of lymph nodes. The 2008 WHO classification on lymphoid neoplasms [2] and Ann Arbor staging [10], the International Prognostic Index (IPI) [5]. The response of the R-CHOP regimen in DLBCL was evaluated base on LUGANO response criteria [11], after 3 cycles and at the end of the treatment by CT scan. Toxicity of R-CHOP regimen was evaluated based on BC Cancer [12]

2.3. Statistical analysis: Statistical analysis was performed with SPSS 20.0

III. RESULTS

3.1. Clinical and paraclinical features

Table 1: Some common characteristics of the study group

Characteristics	n	%
Age		
> 60	15	31.3
< 60	33	68.8
Mean age		52.4
Gender		
Male	27	56.3
Female	21	43.8
Male/female ratio		1.3/1
ECOG		
0-1	43	89.6
2	5	10.4
HBVinfection		
Hepatitis B positive	11	22.9
Hepatitis B negative	37	77.1

Anatomical sites of primary tumors		
Cervical nodes	12	25
Mediastinal nodes	1	2.1
Abdominal nodes	7	14.6
Axillary nodes	3	6.3
Inguinal node	3	6.3
Nasal cavity	2	4.2
Waldeyer's ring	6	12.5
Gastrointestinal tract	5	10.4
Liver	2	4.2
Spleen	2	4.2
Other sites	7	14.6
Stages		
I	3	6.3
II	14	29.2
III	13	27.1
IV	18	37.5

The mean age was 52.4 with majority of patients younger than 60 (69.8%). Male/female ratio = 1.3/1. Most of them had good performance status ECOG (0-1). There were 22.9% cases with hepatitis B positive. The most common primary tumor site was lymph nodes with 54.3%, in which cervical nodes have been found in most of the case. Common extranodal sites involvement was Waldeyer's ring and gastrointestinal tract. Stage IV was found in 37.5% of all cases.

Table 2: NHL classification by WHO 2008

Classification	n	%
Diffuse large B cell lymphoma	28	58.3
Small lymphocytic lymphoma/ chronic lymphocytic leukemia	5	10.4
Mantle cell lymphoma	3	6.3
Follicular lymphoma	3	6.3
Marginal cell lymphoma	1	2.1
T cell lymphoma	8	16.7

Diffuse large B cell lymphoma was the most prominent type accounted for 58.3%, whereas marginal zone lymphoma had the lowest incidence (2.1%)

Table 3: International prognostic index (IPI)

IPI	N	%	Risk groups	n	%
0	2	4.2	Low	21	43.6
1	19	39.6			
2	12	25	Low-intermediate	12	25
3	9	18.8	High-intemediate	9	18.8
4	5	10.4	High	6	12.6
5	1	2.1			

Low risk is the most common group in this research (43.6%), whereas high risk group account 6%, take the lowest position.

3.2. The outcome of the treatment of DLBCL with R-CHOP regimen

There were 25/28 DLBCL patient treated by R-CHOP regimen

Table 4: Response rate of R-CHOP regimen

	CR		PR		SD		PD		Total
	n	%	N	%	n	%	n	%	
After 3 cycles	8	34.8	12	52.2	1	4.3	2	8.7	23
After 6 – 8 cycles	10	58.8	6	35.3	0	0.0	1	5.9	17

There were 23 patients assessed after 3 cycles and this number fell to 17 patients after 6 or 8 cycles because of without completing the treatment. We observed 34.8% patients response completely after 3 cycles and raised to 58.8% at the end of the treatment, after 6 – 8 cycles.

3.3. Toxicities of R-CHOP chemotherapy

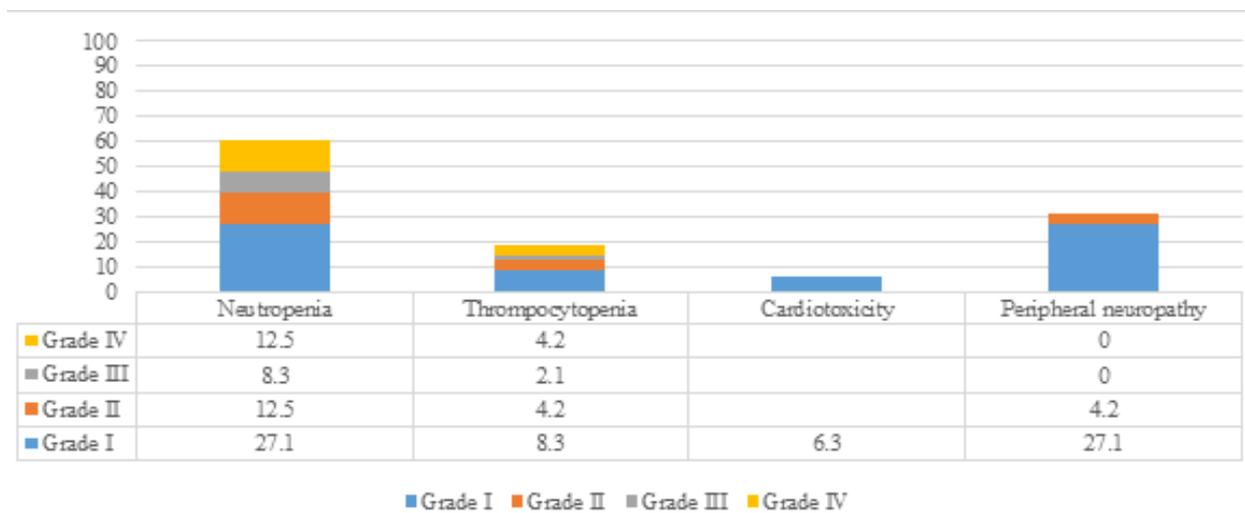|	Neutropenia	Thrombocytopenia	Cardiotoxicity	Peripheral neuropathy
Grade IV	12.5	4.2		0
Grade III	8.3	2.1		0
Grade II	12.5	4.2		4.2
Grade I	27.1	8.3	6.3	27.1

Figure 1: Toxicities

Neutropenia was the most common side effect among 4 assessed catergories with 60.4% while peripheral neuropathy was observed in 31.3% patients. 18.8% of them have presented thrombocytopenia during treatment and cardiotoxicity was experienced in 3 cases, accounted 6.3%.

V. DISCUSSION

Non Hodgkin Lymphoma is a heterogeneous group of B-cell and T-cell neoplasm that arise primarily in the lymph nodes with varied clinical and biologic features. The distribution of NHL types varies internationally. The median

age of NHL in Asian countries is significantly younger, compared to western countries. According to Mohammed AI study in US, mean age was 67 years old [13], whereas it was 56 in Intragumtornchai T's study in Thailand [14]. The mean age in our study was 52.4, quite similar to the result of Vu Duc Binh with 51.3. This disease was more common in male than female with the male/female ratio was almost like Vu Duc Binh study (1.2/1) [7]. DLBCL is the most common Non Hodgkin Lymphoma, accounted for 32.5% among all types of Non Hodgkin Lymphoma in Hamadan Al's study [13]. In this study, the rate of DLBCL was higher than Hamadan Al's study and Vu Duc Binh's study as well (48.3%) [7]. However, in Intragumtornchai T's research on 4056 patients, the rate of DLBCL was 58.1%, quite similar to our study [14]. The percentage of follicular lymphoma (FL) varied significantly between Asian and Western countries. It was found more frequently in US, 17.1% in Hamadan Al's study [13], compared to Thailand, 5.6% in Intragumtornchai T's study [14]. FL rate was also low in our research, we accounted in 3 cases which take 6.3% in all NHL type, lower than Vu Duc Binh's study, 11.1% [7]. Although the exact reason for this difference was unknown, the results of several studies suggested differences in genes and environmental factors such as diet habits, infections and smoking, which plays an important role in follicular lymphoma, were responsible. Some cytogenetic changes such as a higher incidence of BCL-2 translocations were seen more frequently within follicular lymphoma patients in western countries than Asian populations [15]. Small lymphocytic lyphoma/chronic lymphocytic leukemia (CLL/SLL) and FL were similarity in epidemic aspect, the incidence rate in Thailand is 5.2% lower than US – 18.6% [13, 14]. We recorded 5 cases in this study, accounting for 10.4%.

Table 5: The percentage of other NHL types

	Mantle cell	Marginal zone	T/NK cell
Our study	6.3	2.1	16.7
Vu Duc Binh [7]	6.3	5.3	21.3
Intragumtornchai T [14]	2.4	5.9	12.5
Hamadan Al [13]	4.1	8.3	3.6

The proportions of mantle cell, marginal zone and T/NK cell lymphomas were approximately similar between studies except T/NK cell lymphomas rate in Hamadan Al's study was remarkly lower when compare to Asian studies. This variation could reflect exposure or genetic susceptibility to pathogenic agents such as EBV and HTLV1 in Asian countries [16]. Affected sites was seen more frequently in lymph nodes (54.3%) than extra-nodal sites, and cervical lymph nodes took the highest incidence among all lympho nodes, 25%, lower than the research of Vu Duc Binh, lymph nodes take 60.4% of all primary sites and cervical lympho nodes were seen most frequently with 49.8%. Among the extra-nodal sites involved in NHL, Waldeyer's ring was the most common site (12.5%). The second most common site was the gastrointestinal tract (10.4%), whereas nasal cavity (8.2%), tonsial (6.8%), occular cavity (4.8%) and skin are the most common extra – nodal sites in Vu Duc Binh's study [7]. In terms of staging, stage IV took the highest rate with 37.5%, it was similar with Vu Duc Binh's result, 32.4% of all patients are stage IV, stage I was, however, lowest rate in our study (6.3%) but 30.4% in Vu Duc Binh [7]. Our results were quite similar to the reports of Simon, highest in stage IV and lowest in stage I, with 45.7% and 14.0% respectively [17]. We redistributed our patients into four risk groups based on IPI, low risk group registered the highest position with 43.6%, the rates gradually decreased in the poorer prognostic manner which is quite similar to

Ziepert's results, low risk (52%), low - intermediate (21%), high – intermediate (17%) and high risk group (12.6%) [5]. Several researches showed the relation between hepatitis B virus and malignant lymphoma [18, 19]. Feng W reported the HBsAg-positive DLBCL group displayed a younger median onset and more advanced stage at grade III/IV, compared with the HBsAg-negative group [19]. HBV also have impact during chemotherapy via hepatic dysfuntion and virus reactivation. In our study, there were 10 patients have HBV infected condition, taking 22.2% of all the patients in this research.

Table 6: Efficacy of R-CHOP regimen

Study	CR	
	After 3 cycles	**After 6 – 8 cycles**
Nguyen Tuyet Mai [20]	78.2	92.7
Le Trong Thai [21]	36.1	52.8
Coiffier [22]		52
Our study	34.9	58.8

In the total of 48 patients participated in our study, 25 DLBCL patients were treated R-CHOP regimen. However, at the time of assessment, there were only 23 patients followed after 3 cycles and these patients dropped to 17 patients after 6 or 8 cycles (because they are on going treated by chemotherapy). Complete response was found in 34.9% and increased to 58.8% after 6 or 8 cycles. There was a similarity between our study and the results of Le Trong Thai and Coiffier but this research was worse than Nguyen Tuyet Mai's report. This was maybe due to the difference in study samples. There were 52.7% and 63.6% patients in Nguyen Tuyet Mai's research was diagnosed at locally stage (I, II) and low risk group respectively which related to better prognostic and these propotions were higher than our research. Activated B-cell (ABC) type of DLBCL is associated with substantially worse outcomes when treated with standard chemoimmunotherapy, compared to germinal center B-cell (GCB) [23]. In addition to GCB and ABC subtypes, double-hit or triple-hit lymphomas, which overexpress MYC, BCL2 and BCL6 protein, are aggressive DLBCLs and are also associated with a poor prognosis [3]. We assessed 4 common side effects of R-CHOP regimen in this study, neutropenia was seen in 60.4% patients during treatment periods, in which grade 3-4 accounted for 20.8%. Thrompocytopenia happened at the far lower incidence than neutropenia, at 18.8%. Neurotoxicity was quite common with accounted 31.3%, mainly grade 1. Le Trong Thai aslo reported that, neutropenia occurred in 61.1%, in which grade 3 was in 11.1% and there was no case with grade 4 neutropenia [21].

V. CONCLUSION

DLBCL is the most common Non Hodgkin Lymphoma while mantle cell, follicular and marginal zone lymphomas has low incidence rates. *However there need to have futher study.* In terms of response, although there was a small number of followed up patients, R-CHOP regimen could have good results after 6-8 cycles. In addition, to optimize treatment, classification GCB and ABC and developing technique to identify MYC, BCL2 and BCL6 over expression will help to get better prognostic and regimen chosen, increase treatment response.

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