

Available online on 15.12.2020 at <http://jddtonline.info>

# Journal of Drug Delivery and Therapeutics

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Research Article

## Clinicopathological Profile of Low-Grade B Cell Non-Hodgkin Lymphoma in Tertiary Health Care in West Java Indonesia

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### Abstract

**Background:** Low-grade B cell Non-Hodgkin lymphomas (NHL) are a group of lymphomas that are predominantly indolent and make up approximately 50% of all malignant lymphomas. Initial therapy for low-grade B cell LNH has an overall response rate of between 85-94% and a refractory rate of 6-10%. Few reports have been published regarding the clinicopathological characteristics of non-Hodgkin lymphoma cases, especially low-grade B cell types. This research aims to determine the clinicopathological profile of low-grade B cell type non-Hodgkin lymphoma cases.

**Method:** This research is a descriptive study using cross-sectional methods. The sample consisted of 40 low-grade B cell type NHL cases from January 2015 to June 2020 at Hasan Sadikin Hospital, Bandung. Clinicopathological data, including age, sex, location of the tumor (nodal or extranodal), stage, B symptoms, and response to therapy, were taken from the patients' medical records. Data were categorized into 2 groups based on response to initial therapy.

**Results and Discussion:** Of the 40 cases diagnosed with low-grade B cell type NHL, 55% responded to initial therapy. From the non-response group, 61.1% were stage II and 72.2% exhibited B symptoms. There were no significant differences in age, sex, tumor location (nodal or extranodal), stage, or B symptoms in the response and non-response groups.

**Conclusion:** In this study, 45% of patients with low-grade B cell type NHL did not respond to initial therapy. There was no statistically significant difference in the clinicopathological profiles of the response and non-response groups to initial therapy in cases of low-grade B cell type NHL.

**Keywords:** Non-Hodgkin Lymphoma, low-grade B cell lymphoma, therapy response, clinicopathological

Article Info: Received 12 Oct 2020; Review Completed 26 Nov 2020; Accepted 04 Dec 2020; Available online 15 Dec 2020



Cite this article as: Primastari E, Hernowo BS, Dewayani BM, Clinicopathological Profile of Low-Grade B Cell Non-Hodgkin Lymphoma in Tertiary Health Care in West Java Indonesia, Journal of Drug Delivery and Therapeutics. 2020; 10(6-s):89-91 <http://dx.doi.org/10.22270/jddt.v10i6-s.4632>

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### INTRODUCTION

Low-grade B cell non-Hodgkin lymphomas (NHL) are a group of lymphoma subtypes that are predominantly indolent.<sup>1</sup> According to data from GLOBOCAN and Cancer Incidence in Five Continents (CI5), LNH is ranked 5<sup>th</sup> to 9<sup>th</sup> most malignant in countries around the world, with the number of new cases reaching nearly 510,000, and a mortality rate of 14,164 cases in 2018.<sup>2,3</sup> In Indonesia there were 14,164 new cases and 7,565 deaths in 2018.<sup>4</sup> In general, low-grade NHL represent 50% of malignant lymphomas.<sup>5</sup>

The etiology and pathogenesis of low-grade B cell non-Hodgkin lymphoma are associated with Deoxyribonucleic acid (DNA) changes, including gene mutations, amplification, deletions, or chromosomal translocations. The patient's clinical symptoms are usually a painless mass (nodal or extranodal) that enlarges slowly. Occasionally organomegaly, including hepatomegaly and splenomegaly, are found, and occasionally there are non-specific symptoms.<sup>6-10</sup>

Histopathologic and immunohistochemistry (IHC) examinations of CD20, CD3, and Ki67 are used to diagnose low-grade B cell type non-Hodgkin lymphoma. To determine the subtype, further IHC examinations can be conducted for each subtype. The therapeutic modalities used in NHL are chemotherapy, radiotherapy, targeted therapy, and immunotherapy. The therapy used is chosen based on the lymphoma subtype, grading, and staging.<sup>11</sup> The prognosis is generally influenced by the patient's age, clinical signs and symptoms, low-grade B cell NHL subtype, grading, and staging. The majority of low-grade NHL are indolent but generally incurable. In the initial stages of therapy, low-grade NHL are extremely responsive, followed by a relapse-remitting phase with increased resistance to therapy and a shortened response duration.<sup>12</sup>

Articles and data on the clinicopathological characteristics of low-grade B cell non-Hodgkin lymphoma patients in Indonesia are extremely limited. The aim of this research is to provide information on low-grade B cell non-Hodgkin

lymphoma cases in Dr. Hasan Sadikin Central General Hospital in Bandung, West Java, Indonesia.

## MATERIAL AND METHOD

This research is an observational study using cross-sectional methods, examining 40 cases of low-grade B cell type non-Hodgkin lymphoma from January 2015 to June 2020. The research subjects' clinical data were obtained from their medical records, including age, sex, tumor location (nodal or extranodal), stage, B symptoms, and response to therapy. Data on subtype were obtained from histopathological and immunohistochemical examinations by the Dr. Hasan Sadikin Central General Hospital Anatomic Pathology Department. Data were analyzed using IBM SPSS statistics 26.

## RESULTS

The research results highlight demographic data and clinical features as characteristics of the research subjects. Demographic data were taken from 40 research subjects in the age range of 27-77 years, with a mean age of 53.48 and a median age of 55 years. There were a greater number of male than female subjects.

The clinical features of the subjects showed that 72.5% had B symptoms and that the primary tumor was extranodal in 75% of cases. Clinical stages were mostly stage II, with the

smallest number being stage IV. In this study, more cases were in the initial stages (stage I and II) than advanced stages (stage III and IV). Twenty-two of the research subjects responded well (responded) to R-CHOP immunotherapy, while 24 cases were non-responsive.

Cases that were declared as 'responsive' to therapy included those that showed a 'complete response' and 'partial response', while cases with a 'stable disease' and 'progression disease' response were placed in the non-response group. In Table 1, the analysis of the numerical age variable was tested using the unpaired T test. Analyses of the variables of sex, location of the primary tumor, and B symptoms were tested using the chi-square statistical test. Analyses of the Ann Arbor stage and subtype variables were conducted using the Kolmogorov-Smirnov test. The analysis of characteristic variables in Table 1 shows a p-value greater than 0.05, indicating no significant correlation between the characteristic variables of the research subjects and therapeutic response (p-value > 0.05). Based on the test results, it can be concluded that the two groups (response and non-response groups) are the same. In Table 1, it can be seen that cases that did not respond to this study predominantly were male, exhibited B symptoms, in the early clinical stages, and in the marginal zone lymphoma (MZL) subtype, with primary extranodal location of the tumor.

**Table 1. Data Comparison between Characteristics of Study Subjects by chemotherapy response group**

Variable	Therapy response		P value
	Response N=22	Non Response N=18	
<b>Age (years old)</b>			<b>0.926</b>
Mean±Std	53.32±10.580	53.67±12.939	
Median	54.50	56.50	
Range (min-max)	37.00-73.00	27.00-77.00	
<b>Gender</b>			<b>0.071</b>
Male	18(81.8%)	10(55.6%)	
Female	4(18.2%)	8(44.4%)	
<b>Location</b>			<b>0.067</b>
Nodal	8(36.4%)	2(11.1%)	
Extranodal	14(63.6%)	16(88.9%)	
<b>Stage</b>			<b>0.659</b>
I	2(9.1%)	3(16.7%)	
II	10(45.5%)	11(61.1%)	
III	10(45.5%)	3(16.7%)	
IV	0(0.0%)	1(5.6%)	
<b>B symptoms</b>			<b>0.972</b>
Yes	16(72.7%)	13(72.2%)	
No	6(27.3%)	5(27.8%)	
<b>Subtype</b>			<b>0.632</b>
Small lymphocytic lymphoma (SLL)	8(36.4%)	6(33.3%)	
Mantle cell lymphoma (MCL)	1(4.5%)	0(0.0%)	
Follicular lymphoma (FL)	6(27.3%)	2(11.1%)	
Marginal zone lymphoma (MZL)	7(31.8%)	10(55.6%)	

## DISCUSSION

In terms of the characteristic of age, data for each of the study's therapeutical response groups were normally distributed, with a similar mean age, indicating that age was not a confounding factor for the study. In the study, cases of low-grade B cell type NHL were obtained from patients

between the ages of 27 – 77 years, with a mean age of 53 years and a median age of 55 years. The median value is slightly different to the median age of 59 years for low-grade B cell type NHL in countries from the 'far east' category in Perry et al.'s study.<sup>13</sup> In comparison, the median age for low-grade B cell type NHL in developed countries (North America and West Europe) is higher, at 63 years.<sup>13</sup> The difference may

be influenced by differences in population and research sample size.

In this study, data on gender indicated a higher number of males than females (7:3), although statistically insignificant. This finding is similar to the WHO epidemiology and research conducted by Perry et al.<sup>13</sup> which showed a greater number of cases among men than women in both developed and developing countries.

The majority of cases in this study were classed as stage II, at 52.5%, followed by stage I at 12.5%, stage III at 32.5% and stage IV at 2.5%. A retrospective study by Ciobanu et al.<sup>14</sup> produced different results, with 83.3% of cases being stage III-IV. This is possibly due to the majority of cases included in the study exhibiting B symptoms, despite being detected in the early stages. In stage I, up to 20% (1/5) of cases were accompanied by B symptoms, 90.5% (18/21) in stage II, 61.5% (8/13) in stage III, and 100% (1/1) in stage IV. It is possible that many of the cases were detected in the early stages due to the emergence of B symptoms, leading the patients to seek healthcare services. If viewed by subtype, 10/14 SLL cases (71.4%) exhibited B symptoms, in contrast to research conducted by Mukkamalla SKR et al.<sup>15</sup> which found that only 5 – 10% of patients with SLL experienced B symptoms. This finding was the same for Marginal Zone Lymphoma (MZL), with 58.8% (10/17) of cases in the study exhibiting B symptoms. According to the WHO, approximately 10 -20% of MZL experience B symptoms. All cases (9/9) of follicular lymphoma in this study experienced B symptoms. Meanwhile, according to the WHO, B symptoms rarely occur in MZL. B symptoms are associated with an increase in inflammatory proteins in the plasma that are related to poorer response to chemotherapy and survival rate than patients with normal inflammatory proteins in the plasma.<sup>16</sup> In this study, B symptoms had no significant relationship with immunochemotherapy response to R-CHOP.

The cases used as subjects in this research were all immunohistochemically diagnosed as B cell type NHL (CD20 positive, CD3 negative) and had a Ki67 proliferation index of below 30% (low grade). Some of the most common B cell type NHL subtypes are follicular lymphoma (FL), marginal zone lymphoma (MZL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and mantle cell lymphoma (MCL). In this research, the majority of cases fell under the MZL subtype (42.5%), followed by SLL (35%), FL (22.5%) and MCL (2.5%). This finding deviates from the results of a study conducted by Perry et al.<sup>13</sup>, which found that from the low-grade B cell type NHL group, FL was the largest subtype, followed by MZL (MALT and Nodal), MCL and lastly SLL/CLL. This difference may be due to differences in population and sample size. For example, the study conducted by Perry et al. found differences in subtype percentage between asia and western countries, including that there were significantly more cases of MZL and fewer FL and MCL in asia countries

According to data on responses to R-CHOP immunochemotherapy from this study, 55% of cases responded to R-CHOP immunochemotherapy. In a study by Walewski et al.<sup>17</sup>, indolent lymphoma therapy using R-CHOP had an overall response rate (complete and partial response) of 94.5%. This difference in findings may be due to differences in the characteristics of the low-grade B cell type NHL populations.

**Acknowledgment:** We thank the Anatomical Pathology Department Padjdjaran University and Medical Record Department Hasan Sadikin central general hospital Bandung for helping us to do this research.

**Conflict of Interest:** The authors declare no conflict of interest.

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