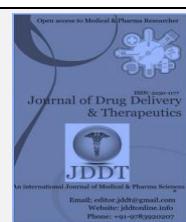
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Research Article

Clinicopathologic Characteristics and Chemotherapy Response of Classic Hodgkin Lymphoma: A Study in Tertiary Teaching Hospital

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Abstract

Background and Objective: Hodgkin Lymphoma (HL) is known as a malignancy of the lymphatic system and 90% of the HL is Classic Hodgkin Lymphoma (CHL). Prognostic factors that identify the patient's response to therapy are useful for optimizing the therapy. This study aims to assess the clinicopathological characteristics and chemotherapy response associated with CHL patients.

Materials and Methods: This is a retrospective study of 40 patients diagnosed as CHL and treated with ABVD chemotherapy at Hasan Sadikin General Hospital/Padjadjaran University, Bandung, Indonesia during the period of January 2014 to December 2019. The clinicopathological characteristics data consisting of age, sex, histopathology subtype, tumor location and clinical stage were assessed. Their responses to chemotherapy were also analyzed.

Result and Discussion: A total of 40 patient data were included in this study, 21 CHL patients responded to ABVD chemotherapy (52.5%) while 19 patients not responded (47.5%). There were no significant association between age, sex, histopathological subtype, tumour location and clinical stage with chemotherapy response.

Conclusion: In this study, 47.5% of CHL patients did not respond to ABVD chemotherapy. The response of ABVD chemotherapy was not associated with age, sex, histopathological subtype, tumor location or clinical stage.

Keywords: Classic Hodgkin Lymphoma, chemotherapy response, clinicopathological characteristics.

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INTRODUCTION

Hodgkin Lymphoma (HL) is a lymphoid neoplasm that generally occurs in the lymph nodes. HL consists of mononuclear and multinucleated cells with a background of mature, non-neoplastic inflammatory cells¹. Based on data from the GLOBOCAN International Agency for Research on Cancer (IARC) in 2018, HL has an incidence rate of 0.44% of all malignant cases². In Indonesia, the percentage of new cases is 0.3% and the mortality rate is 0.28%³.

Based on the histopathological appearance, HL is divided into 2 types known as Classic Hodgkin Lymphoma (CHL) which has Hodgkin-Reed-Sternberg (HRS) cells and the Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) which is dominated by lymphocytes. CHL includes 90% of the total HL cases. CHL is subdivided into four main

histologic subtypes: nodular sclerosis, mixed cellular, lymphocyte-rich and lymphocyte depleted¹.

Patients who have been given first line chemotherapy (CT) in CHL have more than 80% of cases enter into complete remission, however up to 40% become relapses and about 10-25% experience refractory or unresponsive, thus requiring additional therapy⁴⁻⁶.

The patient's outcome can be determined by the characteristics of the disease. The presence of prognostic factors should help to stratify therapy according to risk profiles and predict which patients may fail therapy⁷. In developing countries, limited information is available on clinical, epidemiological, or response to the therapy. The current study aims to investigate clinicopathology figures and chemotherapy response in patients with CHL in our tertiary centre.

MATERIAL AND METHODS

This research was a retrospective analytic-observational study of 40 patients diagnosed as CHL during in period 2014-2019 in Department of Anatomical Pathology, Hasan Sadikin General Hospital/Padjadjaran University, Bandung, Indonesia. The study group involved patients were aged from 13 to 76 years which consists of 22 males and 18 females. Ethical approval was given by the General Hospital. Clinicopathological parameters included in the analysis were age, sex, histological subtype, stage, tumour location and chemotherapy response. Data processing used the Statistical Package for Social Science (SPSS) software for Windows operating system.

The ABVD regimen was started initially in each patient regardless of staging status. Chemotherapy response assessments were carried out after at least 4 cycles of CT. Patients that received radiotherapy were not included in the object of study. Complete Remission (CR) was defined as the complete regression of clinical and radiological lesions. Partial Response (PR) was defined as the reduction of the lesion size $\geq 30\%$ from the total longest diameter of the target lesion. Progression of Disease (PD) was defined as increase by $\geq 20\%$ of at least one measurable lesion, or by the appearance of a new lesion. Stable Disease (SD) was defined as decreased or increased size of lesions that do not qualify for PR or PD⁸. All cases were declared to respond to chemotherapy if they were included in the complete or partial response criteria, and as non-responsive if they were included in PD or SD criteria.

RESULTS

Table 1 shows the patient characteristics, the mean age of 39 years. There are more subjects under 45 years of age. The male gender is more than the female. Most histopathology subtype was MCCHL (37.5%). Most clinical stage is stage II (35%). The most common tumor sites were nodal in 77.5%.

All patients were evaluated for treatment response as shown in Table 2. After 4-cycles of CT, 21 patients (52.5%) showed responsive groups (complete and partial response) and 19 patients (47.5%) non-responsive groups (stable and progression). As shown in Table 2, there were association between the characteristics of study subjects by age, age category, sex, histopathological subtype and clinical stage in the responsive and nonresponsive groups. Numerical data analysis was tested by using unpaired T test.

The group of nonresponsive subjects result mean age value of 38 years. The age category < 45 years has a higher

percentage of 68.4%. Gender is more common in women (57.9%). Most histopathology subtype was MCCHL (42.1%). For the most clinical stages, there are stages II and IV with the same percentage (36.8%). While in the group that responded to chemotherapy, the most often was stage II. At tumor site, both groups were consistently nodal. The analysis in Table 2 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).

Table 1. Characteristic of patients

Variable (N=40)	
Age (year)	
Mean \pm Std	39.18 \pm 16.356
Age category (year)	
<45	26 (65%)
≥ 45	14 (35%)
Sex	
Male	22 (55%)
Female	18 (45%)
Histopathological subtype	
NSCHL	13 (32.5%)
MCCHL	15 (37.5%)
LRCHL	8 (20%)
LDCHL	4 (10%)
Stage	
I	4 (10%)
II	14 (35%)
III	12 (30%)
IV	10 (25%)
Location	
Nodal	31 (77.5%)
Ekstranodal	9 (22.5%)

Table 2. Association of chemotherapy response on CHL with characteristic of patients (NR = Nonresponsive; CR/PR = Complete response/ Partial response)

Variable	Chemotherapy response groups		p-value
	NR N=19	CR/ PR N=21	
Age (year)			
Mean±Std	38.47±15.756	39.81±17.244	
Age category (year)			
<45	13 (68.4%)	13 (61.9%)	
≥45	6 (31.6%)	8 (38.1%)	
Sex			
Male	8 (42.1%)	14 (66.7%)	
Female	11 (57.9%)	7 (33.3%)	
Histopathologic subtype			
NSCHL	6 (31.6%)	7 (33.3%)	
MCCHL	8 (42.1%)	7 (33.3%)	
LRCHL	4 (21.1%)	4 (19.0%)	
LDCHL	1 (5.3%)	3 (14.3%)	
Clinical stage			
I	1 (5.3%)	3 (14.3%)	
II	7 (36.8%)	7 (33.3%)	
III	4 (21.1%)	8 (38.1%)	
IV	7 (36.8%)	3 (14.3%)	
Tumor location			
Nodal	14 (73.7%)	17 (81.0%)	
Ekstranodal	5 (26.3%)	4 (19.0%)	

DISCUSSION

CHL accounts for 90% of all Hodgkin lymphoma cases. Based on WHO data, the average age of CHL patients has a bimodal age distribution in early adulthood are 20-30 years and more than 55 years (advanced adults)¹. The age of patients in this study were ranged from 13-76 years with a mean age of 39 years. The youngest age in this study was slightly lower than Gerber *et al*'s research report, which represents the age range of 24-51 years⁹. CHL is more common in children in developing countries. While in developed countries, it is more dominated by young adults who occur increases with age¹⁰.

At age ≥ 45 years, they were usually less response to chemotherapy due to the lack of ability to tolerate chemotherapy doses⁷. In this study, it was found that the variable age ≥ 45 years had a number of cases that did not differ too much between the responded group and those who did not. There were 8 cases who responded, with age ≥ 45 years (5 patients were under 60 years old). It was known that the response to chemotherapy decreases with age, especially > 60 years due to more frequent use of comorbid diseases and the higher likelihood of toxicity¹¹.

It was found that the highest number of cases were male patients (55%), this is similar to the epidemiology in WHO and other studies^{1, 9, 12}. According to Moccia *et al*, male tended to be independently associated with a poorer outcome¹³. However, women represented a higher percentage in the group who did not respond to chemotherapy in our study. The different responses of male and female to lymphoma may be due to differences in pharmacokinetics. Female patients were known to be more haematological toxicity, more often with leukopenia⁷.

The most histopathological subtype in this study was MCCHL at 37.5% and the second largest was NSCHL at 32.5%. Similar results were obtained in a study conducted by Mozahab *et al* for Asian population, and the study of Konkay *et al* in one of the institutions in India^{14, 15}. This was consistent with previous studies which reported that MCCHL was more common in developing countries¹⁶. Whereas in western countries, the most subtypes were in the NSCHL subtype^{1, 17}. It was shown that MCCHL was also the most common in the nonresponsive group, although it was not statistically significant. MCCHL is often associated with a poor prognosis, this was possible because MCCHL was more common in the elderly and was found at more advanced stages⁴.

The result showed the most cases of CHL were included in stage II (35%). This result was similar with previous study by Boo *et al.* in one hospital in Malaysia¹⁸. Based on a retrospective study in 3 hospitals in Saudi Arabia by Shafi *et al.*, the results were slightly different. It showed 74% of cases were at stage III-IV¹⁹. This was possible due to the patient's lack of knowledge about lymphoma, so they did not immediately seek treatment when symptoms appeared. The lack of early detection of lymphoma in Indonesia has also affected the number of cases found at an early stage. CHL patients with an advanced stage, who had been given chemotherapy treatment, were associated with shorter progression free survival. It was related to patients who experience amplification of chromosome 9p24.1. It has been stated by previous studies, that increasing the amplification of chromosome 9p24.1 will increase the expression of PD-L1 on the surface of HRS cells, so that it is expected to have a better outcome after PD-1 blockade⁴.

The number of patients with nodal sites were more cases when compared to extranodal sites. In the CHL, almost all cases were found in the lymph nodes, although in the course of the disease it can develop into extranodes. Extranodal invasion of adjacent tissues may occur in up to 15% of cases²⁰. The percentage of case responded to the chemotherapy regimen (CR/PR) in this study was lower than other study response²¹⁻²³. This difference was due to the number of the samples and includes radiotherapy as an adjunct therapy, which may have contributed to the successful response to therapy.

CONCLUSION

There were 47.5% of patients not responding to chemotherapy, with the most common histopathologic subtypes was MCCHL and stage II. There was no statistically significant association between clinicopathological characteristics with chemotherapy response.

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CONFLICT OF INTEREST

The authors declare that there are no conflict of interests in this study.

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