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THE CORRELATION BETWEEN CELL OF ORIGIN SUBTYPE WITH OVERALL SURVIVAL OF DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS IN KARIADI GENERAL HOSPITAL SEMARANG

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ABSTRACT

Background: DLBCL is the most common type of NHL in the world. DLBCL based on cell of origin is divided into GCB and non-GCB. The diagnosis of DLBCL has not been routinely done to its cell of origin, and there have not been many studies that discuss the DLBCL subtype and the overall survival of the patients, especially in Kariadi General Hospital. This study aims to determine the correlation of DLBCL cell of origin with the 2-year overall survival of DLBCL patients in Kariadi General Hospital. **Methods:** This is an observational analytic study of 40 DLBCL patients in Kariadi General Hospital from January to August 2017. The data collection including: age of diagnosis, location, stage and 2-year overall survival. Data analysis used chi square test and Kaplan Meier curve. **Results:** GCB patients had higher 2-year overall survival than non-GCB subtype significantly (p: 0.047), with a 2-year survival rate of GCB subtype was 66.7% and non-GCB subtype was 31.6%. GCB patients tend to have early stage than non-GCB subtype significantly (p:0.028). **Conclusion:** DLBCL GCB subtype patients had significantly higher 2-year overall survival therefore it has better prognosis than non-GCB subtype.
Keywords: DLBCL, GCB, non-GCB, overall survival

INTRODUCTION

Lymphoma is a malignancy arisen from lymphoid tissue, divided into two main groups: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL).[1] In Indonesia, NHL is the seventh most common cancer.[2] The most common type of NHL in Asia including Indonesia is Diffuse Large B-Cell Lymphoma (DLBCL), about 30-40%.[3–6]

DLBCL is an aggressive B-cell NHL with a diffuse growth pattern.[7] Based on the molecular profile of the original cell (Hans criteria), DLBCL is classified into 2 subtypes, Germinal Center B-cell type (GCB) and Activated B-Cell type (ABC) or non-Germinal Center B-cell type (non-GCB), using immune-profile using immunohistochemistry examination of CD10, BCL6 and MUM1.[8,9] In general, DLBCL GCB subtype has better prognosis and overall survival compared to non-GCB subtypes.[10,11]

Case data of DLBCL in Indonesia have not been well developed and published. Making diagnosis of DLBCL case in Indonesia, especially in Kariadi General Hospital, has not been done into its molecular subtype because of lacking immunohistochemistry examination. Making complete diagnosis of DLBCL into its molecular subtype is very important to support immunotherapy and predict prognosis of DLBCL patient. This study aims to determine the relationship of DLBCL cell of origin with the 2-year overall survival of DLBCL patients in Kariadi General Hospital.

METHODS

This is an observational analytic study with cross sectional design. Samples were DLBCL patients who had been diagnosed as DLBCL based on histopathological and immunohistochemical examinations, which showed diffuse CD20 and high Ki-67

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expression, in Anatomical Pathology Laboratory of Kariadi General Hospital, Semarang, which is top referral hospital in Central Java, Indonesia, in the period of time from January to August 2017. A total of 40 patients were included in this study and were followed for 2 year after diagnosis and treatment to determine 2 years overall survival.

Clinical feature of samples taken include: age of diagnosis which categorized into > 50 years and <50 years, tumor location which categorized into nodal and extranodal, tumor stage using Ann Arbor staging which categorized into the early stage (stage I and II) and advanced stages (stage III and IV), cell of origin subtypes based on immunohistochemical examination of CD10, BCL6 and MUM1. DLBCL patients were categorized as GCB type if show immune-profile CD10(+)/(-), BCL6(+) and MUM1(-), while categorized as non-GCB type if show immune-profile CD10(-), BCL6(+)/(-) and MUM1(+). Overall survival of the patient is described as how many months they were survived after diagnosis with end of observation until August 2019. Data analysis using chi square test with a significance level <0.05, and survival analysis using Kaplan Meier curve.

RESULT

40 DLBCL patients at Kariadi General hospital was included in this study, equally diagnosed at the age about 51-year-old (51.15 ± 13.20) and more often had a primary extranodal location (70%). The location of extranodal tumors in these patients include: tonsils, palpebra, nasopharynx, gastrointestinal tract, liver, spleen, kidney, nasal cavity, mammae, conjunctiva, central nervous system and femur, while the location of nodal tumors is found in colli, inguinal, axillary and intraabdominal, mediastinum and pelvic lymph nodes which can be single or multiple. Based on Ann Arbor Staging, from 40 DLBCL patients in Dr. Kariadi was mostly diagnosed at an early stage (60%).

Table 1. clinicopathological features of DLBCL patients (n = 40)

	Frequency	**Percentage**	**Mean ± SD**
Age of diagnosis			51,15 ± 13,20
			(24 – 77 y.o)
Age category			
< 50 y.o	20	50%	
> 50 y.o	20	50%	
Location			
Nodal	12	30%	
Ekstranodal	28	70%	
Stage			
Early (I & II)	24	60%	
Advance (III & IV)	16	40%	
Cell of origin subtype			
GCB	21	52,5%	
Non-GCB	19	47,5%	
2 years overall survival			
Survive	20	50%	
Death	20	50%	

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Based on the cell of origin subtype of DLBCL, from 40 DLBCL patients, divided into 21 patients (52.5%) had a GCB subtype and 19 patients (47.5%) had a non-GCB subtype. After 2 years follow-up after diagnosis and treatment, from 40 DLBCL patients, 20 patients (50%) died within the first year.

Table 2. Correlation between age of diagnosis, location and stage with cell of origin subtype of DLBCL

	GCB	Non-GCB	p
Age of diagnosis			0.342
< 50 y.o	12 (57.1%)	8 (42.1%)	
> 50 y.o	9 (42.9%)	11 (57.9%)	
Location			0.240
Nodal	8 (38.1%)	4 (21.1%)	
Ekstranodal	13 (61.9%)	15 (78.9%)	
Stage			0.028
Early (I & II)	16 (76.2%)	8 (42.1%)	
Advance (III & IV)	5 (23.8%)	11 (57.9%)	

Among DLBCL GCB subtype patients in this study, 57.1% were diagnosed at less than 50 years of age, 61.9% have extranodal location and 76.2% were present at an early stage, whereas DLBCL patients were non-GCB subtype, 57.9% were diagnosed at more than 50 years of age, 78.9% are located extranodal and 57.9% present at an advance stage. There were no significant differences and correlation between age of diagnosis and location with cell of origin subtype of DLBCL. There was significantly difference and correlation between stage with cell of origin subtype of DLBCL.

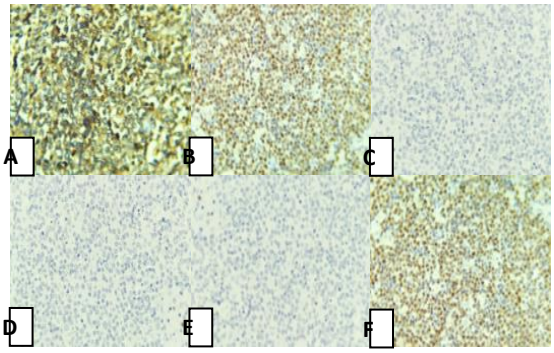

Figure 1. A. CD10 positive in DLBCL GCB type. **B**. BCL6 positive in DLBCL GCB type. **C.** MUM1 negative in DLBCL GCB type. **D**. CD10 negative in DLBCL non-GCB type. **E.** BCL6 negative in DLBCL non-GCB type. **F.** MUM1 positive in DLBCL non-GCB type

In the survival analysis, it showed that DLBCL GCB subtype patients had higher overall survival (66.7%) compared to DLBCL non-GCB subtype (31.6%) significantly based on log-rank test, with median survival of non-GCB DLBCL patients is 5 months.

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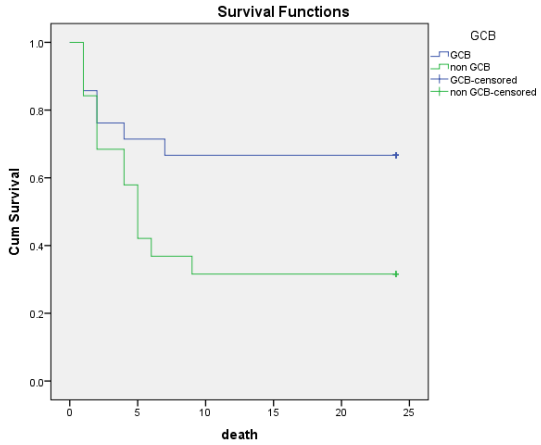

Figure 2. 2-year overall survival DLBCL patient based on cell of origin subtype (GCB vs non-GCB)

DISCUSSION

40 DLBCL patients at Kariadi General Hospital Semarang in the period of January 2017 to August 2017, followed for the next 2 year to find out 2 year overall survival and clinical factors that influence it, which includes the patient's age of diagnosis, location of the tumor (nodal / extranodal), tumor stage based on Ann Arbor staging system and cell of origin subtype (GCB / non-GCB subtype) using immunohistochemistry examination. Based on previous study, patients with DLBCL in the world have an average age of diagnosis in older age with a median age in the sixth decade, but can also appear at a younger age.[12–14] Previous study in Indonesia reported most DLBCL patients were diagnosed at 45 to 64-year-old.[15] It is consistent with this study where the age of diagnosis of DLBCL patients at Kariadi General Hospital Semarang is approximately 51-year-old, with the youngest age 24-year-old, and the oldest age is 77-year-old. The GCB sub-type DLBCL patients in this study were more diagnosed at the age of less than 50-year-old, while the non-GCB subtype DLBCL patients were more diagnosed at the age more than 50-year-old, but there were no significant differences were found between age of diagnosis and cell of origin subtype of DLBCL in this study. This is in line with previous studies that there were no significant differences and correlation between age of diagnosis with cell of origin of DLBCL.[10,16,17]

Location of DLBCL patient's tumor in this study, either GCB or non-GCB subtype, 70% located extranodal, therefore there were no significant differences were found between location of the tumor and cell of origin subtype of DLBCL. The most common tumor sites were colli, tonsils and inguinal. In previous studies, primary extranodal DLBCL was more common happened and had no significant differences between location of the tumor and cell of origin subtype of DLBCL which is in line with this study.[18–20]

Frequency of DLBCL patients who diagnosed at advance stage were slightly higher (60%) than those who diagnosed at early stage (40%), but in previous studies most DLBCL patients were diagnosed at early stage.[12,13,21] GCB subtype DLBCL was often found at early stage (76.2%), while non-GCB subtype DLBCL was often found at advance stage (57.9%) because gene mutation level of non-GCB subtype is higher than GCB subtype. Thus, there is possibility that non-GCB patients came with advance stage comparing to GCB subtype patients.

Cell of origin subtype of DLBCL patients had slightly same proportion between GCB subtype (52.5%) and non-GCB subtype (47.5%). In previous studies, the frequency difference between GCB and non-GCB subtype was uncertain depends on geographical location and race's characteristic.[22,23]

GCB subtype patients in Kariadi General Hospital significantly had higher overall survival (66.7%) than non-GCB subtype patients (31.6%) which is in line with previous studies.[16,24,25] Compared to previous study, appears that overall survival of GCB subtype DLBCL in this study slightly lower

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than GCB subtype DLBCL in other study (66.7% vs 68%).[26] Most studies showed that GCB subtype DLBCL has higher proliferation and apoptotic index than non-GCB subtype which is caused by overexpression of CD10 and BCL6 in GCB subtype. Thus, GCB subtype patients were more sensitive toward the therapy than non-GCB subtype patients which made GCB subtype patients had higher prognosis than non-GCB subtype patients.[21,25,27,28] DLBCL patients with non-GCB subtypes are known to have a worse prognosis. This is related to the presence of more mutations in the non-GCB subtype DLBCL than the number of mutations in the GCB subtype. In the non-GCB subtype DLBCL there are at least mutations found in 20 growth regulating genes, namely BCL6, INK4, PRDM1, TNFAIP3, SPIB, CARD11, MYD88, MYC / BCL2, NFKB, CD79A, CD79B, CREBBP, E300, MLL2, MEF2B, MEF2B, TBL1, , NOTCH1, NOTCH2, BRAF and TP53, while in DLBCL GCB subtypes there were at least mutations found in 7 growth regulating genes, namely BCL2, EZH2, CREBBP, TNFRSF14, GNA13, SGK1 and C-REL.[29–31]

CONCLUSION

DLBCL patients with GCB subtypes had significantly higher 2 years overall survival than non-GCB subtypes (66.7% vs 31.6%) significantly (p: 0.047).

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