Correlation between C-MYC and BAX expression with various Ann Arbor stages in B-cell large cell type of Non-Hodgkin lymphoma

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RESEARCH ARTICLE

Correlation between C-MYC and BAX expression with various Ann Arbor stages in B-cell large cell type of Non-Hodgkin lymphoma

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ABSTRACT:

Diffuse large B-cell lymphoma (DLBCL) is one of the B-cell large cell types of non-Hodgkin lymphoma (NHL) that has poor prognosis with highly variable clinical course. Various prognostic factors have been proposed to predict this, but the results were variable. *C-MYC* is a proto-oncogen that can cause overexpression leading to the increased of tumor cells proliferation. BAX is a main proapoptotic member of the BCL-2 family proteins that regulates apoptotic function. The study aimed to analyze correlation of c-MYC and BAX protein with various Ann Arbor stages in B-cell large cell type of NHL. This cross-sectional study was performed on 39 formalin fixed paraffin-embedded tissue of patients diagnosed as B-cell large cell type of NHL during January 2017 - December 2019 in Anatomical Pathology Laboratory at Dr. Soetomo General Hospital, Surabaya. To assess the expression of c-MYC and BAX, the immunohistochemistry examination was performed. Immunoexpression of C-MYC and BAX were evaluated according to the number of positive tumor cells divided by the total number of tumor cells and calculated in percentage. There was no difference in C-MYC ($p = 0.877$) and BAX ($p = 0.093$) expression with various Ann Arbor stages in B-cell large cell type of NHL. There was no correlation between c-MYC with BAX expression in various Ann Arbor stages in B-cell large cell type of NHL ($r_s = 0.206$, $p = 0.209$). This indicated that C-MYC and BAX expression alone could not to be used as parameters to predict the outcome of the B-cell large cell type of NHL via Ann Arbor stages.

KEYWORDS: B-cell large cell type of NHL, c-MYC, BAX, Ann Arbor staging.

INTRODUCTION:

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy in the worldwide[1]. There is a significant increase in the prevalence of lymphoma per 100,000 population, which made NHL one of the most important malignancies and has contributed to the increased prevalence of malignancy. In Indonesia, non-Hodgkin lymphoma, Hodgkin lymphoma and leukemia are the sixth rank of malignancy[2]. The most common type of NHL is DLBCL[3].

The history of patients, physical examination, laboratory tests, and radiological examination can be done to determine the anatomic staging of NHL, in addition to definitive evidence by biopsy. The Ann Arbor staging is based on the pattern of tumor spread and this staging is important for standard management in lymphoma, as it plays role in patients' treatment selection and can help to stratify patients according to the risk factor profiles. The Ann Arbor staging system is considered simple and concise to use for NHL staging[4,5]. Determination of NHL diagnosis at Dr. Soetomo General Hospital, Surabaya is carried out through the careful of anamnesis, physical examination and radiological examination via USG and CT-scan for staging based on the Ann Arbor system.

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Cellular and molecular variation underlying DLBCL are also important as the prognostic variables. Gene translocation and/or C-MYC overexpression in DLBCL have been intensively researched and can be used as the prognostic markers[6]. C-MYC overexpression can activate the transcription of several genes causing in increased of tumor cells proliferation[7]. Apoptosis can also be induced by overexpression of C-MYC. C-MYC overexpression causes the activation of ARF-p53 pathway, resulting in increased of BAX protein and then occurs apoptosis[8]. If there is no apoptosis, then it will cause the proliferation of tumor cells and chemotherapy resistance[9].

At this time, studies of c-MYC and BAX expression related to the clinical stages of NHL are still limited, especially in Indonesia. This study aimed to analyze the correlation of c-MYC and BAX expressions with various Ann Arbor stages in B-cell large cell type of NHL.

MATERIALS AND METHODS:

Research design:

This study was an observational analytic study with cross-sectional approach. Samples in this study were 39 paraffin blocks from patients diagnosed as B-cell large cell type of NHL during January 2017 until December 2019 in Anatomical Pathology Laboratory at Dr. Soetomo General Hospital, Surabaya, which met the inclusion criteria. The Ann Arbor stages assessment was performed by collecting data via medical records which included patient's clinical data and radiological examination.

Immunohistochemistry staining:

Immunohistochemistry staining was performed to detect the expression of C-MYC and BAX. The block samples of paraffin were cut into 4µm sections with microtome, deparaffinized three times using xylol each for 5 minutes then rehydrated using 96%, 90% and 80% ethanol, each for 2 minutes. Slides were immersed into the 3% hydrogen peroxide for 15 minutes, then warmed using *Target Retrieval Solution* (TRS)/*buffer citrate* at pH of 6 in the microwave for 15 minutes and washed with PBS for 5 minutes. After that, the tissue sections were incubated with monoclonal antibodies for c-MYC (dilusion 1:100, Biocare Medical) and BAX (dilusion 1:100, Boster Biological Technology) overnight. Secondary antibody was applied for 10 minutes at room temperature. Meyer Hematoxylin was used to counterstain the sections. Last process was dehydrated with 95% alcohol. This study had been approved by the Committee of Health Research Ethic at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (0451/LOE/301.4.2/IV/202).

Evaluation of immunohistochemistry expression:

C-MYC was positive if expressed in ≥ 40% of tumor cells nuclei and negative if expressed in < 40% of tumor cells nuclei. While BAX was considered positive if expressed in tumor cells cytoplasm.

Statistical analysis:

SPSS sofware was used to process the data obtained. The imunoexpression of c-MYC was statistically analyzed using Mann Whitney test and BAX using independent sample T-test. Correlation between c-MYC and BAX were analyzed using Spearman test.

RESULTS AND DISCUSSION:

Most samples in this study were aged between 61 to 70 years, with the mean age was 55.18 years. Most samples (64.1%) were male (25 samples). The location of the samples in this study mostly were from the neck lymph node (43.6%, 17 samples), and (17.9%, 7 samples) were from extranodal location. Most samples (30.8%) were in stage IIIB of Ann Arbor (12 samples). The distribution of the samples according to Ann Arbor stages are described in Table 1. The samples in this study used the Ann Arbor staging classification which were divided into 4 stages. Ann Arbor staging classification was used to divide according to the absence (A) or presence (B) of B-symptoms related to the disease, such as: fever with temperature > 38°C, sweating at night, and within 6 months of weight loss > 10%[10].

Table 1. Distribution of the samples according to Ann Arbor stages

Ann Arbor stages	Number of cases
IA	3
IB	6
IBE	6
IIA	1
IIB	6
IIBE	1
IIIA	2
IIIB	12
IIIBE	1
IVA	1
IVB	0
Total	39

The stages group above were grouped again into limited stages (stages I and II) and advanced stages (stages III and IV), with or without clinical symptoms (B-symptoms). Limited stage was the most stage in this study (59%, 23 samples).

C-MYC expression is depicted in Figure 1. Based on Mann Whitney test, there was no difference of c-MYC expression with various Ann Arbor stages in B-cell large

cell type of NHL (p = 0.877) (Table 2). Based on Spearman correlation test, there was no significant correlation of c-MYC expression with various Ann Arbor stages in B-cell large cell type of NHL (p = 0.877). These results showed that c-MYC expression was not related to clinical stages in B- cell large cell type of NHL ($p > 0.05$) (Figure 3A).

BAX expression is depicted in Figure 2. Based on independent sample T-test, there was no difference of BAX expression with various Ann Arbor stages in B-cell large cell type of NHL (p = 0.093) (Table 3). Based on Pearson correlation test, there was no significant correlation of BAX expression with various Ann Arbor stages in B-cell large cell type of NHL (p = 0.093). These results showed that BAX expression was not related to the clinical stages in B- cell large cell type of NHL (p > .05) (Figure 3B). There was no correlation between c-MYC and BAX expressions (p = 0.209) (Figure 3C). This indicated that the level of c-MYC expression did not affect the BAX expression in various Ann Arbor stages in B-cell large cell type of NHL.

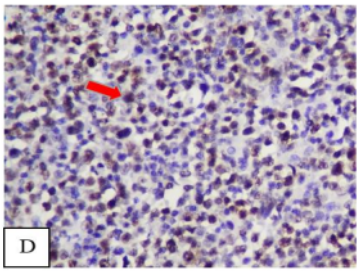
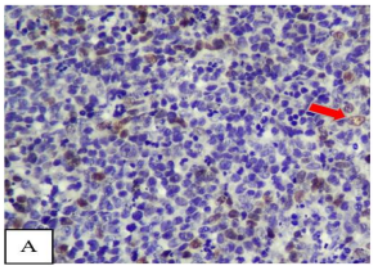
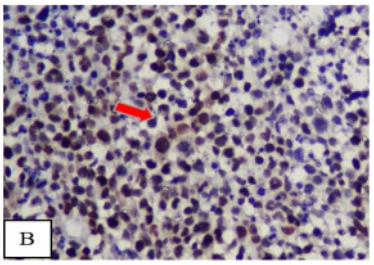


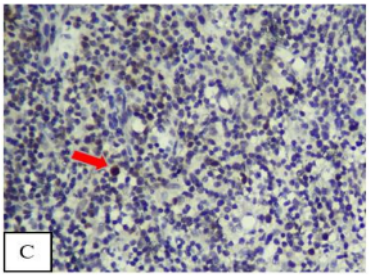
Figure 1: C-MYC expression in the nucleus of tumor cells (red arrow). C-MYC expression in limited stage (A and B). A: Expressed in 25% of tumor cells; B: Expressed in 65% of tumor cells. C-MYC expression in advanced stage (C and D). C: Expressed in 20% of tumor cells; D: Expressed 60% of tumor cells (all in 400x magnification).

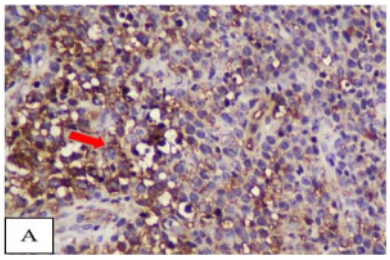
Table 2. C-MYC expression in various Ann Arbor stages of B-cell large cell type of NHL

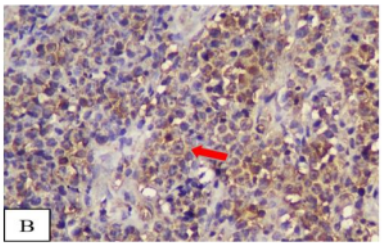
Ann Arbor Stages	c-MYC expression		Min	Max	Median	*p*
	Positive	Negative				
Limited	10 (25.6%)	13 (33.3%)	3.3	85	30	0.877
Advanced	7 (17.9%)	9 (23.1%)	7.5	70	27.5	

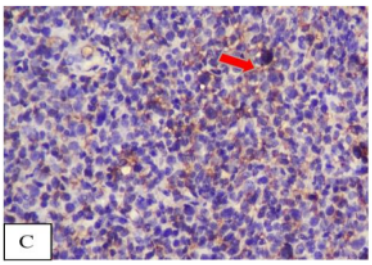












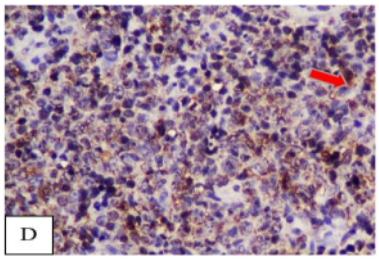


Figure 2: BAX expression in the cytoplasm of tumor cells (red arrow). BAX expression in limited stage (A and B). A: Expressed in 65% of tumor cells; B: Expressed in 85% of tumor cells. BAX expression in advanced stage (C and D). C: Expressed in 65% of tumor cells; D: Expressed 60% of tumor cells (all in 400x magnification).

The Ann Arbor staging system is based on the pattern of tumor spread and this staging is important for standard management in lymphoma. This staging is divided into 4 stages. Stage I and II may be different in some situations but both have the same treatment. The same therapy is also performed to the patients in stage III and IV. Thus, there is a basis for reclassifying as limited (stages I and II) or advanced stage (stages III and IV) for therapy purposes[10]. The Ann Arbor staging classification is used to divide based on the absence or presence of B-symptoms related to the disease, but the clinical stages are often not recorded or inaccurate. The clinical stages do not appear to be related with the prognostic outcome. Therefore, the clinical stages do not need to be applied because they do not affect the management of NHL patients[5].

C-MYC is a proto-oncogene and transcription factor that can regulate the cell proliferation, metabolism, differentiation, and apoptosis. The poor prognosis in NHL caused by overexpression and translocation of *c-MYC* because of *MYC-IGH* chromosome rearrangement[11]. Activation of several signaling pathways can also induce the upregulation of c-MYC expression resulting in tumor cells proliferation[12].

This study showed that there was no difference of c-MYC expression with various Ann Arbor stages in B-cell large cell type of NHL. The result of this study may be because the limited and advanced of Ann Arbor stages do not determine the aggressiveness of a disease, but the clinical stages are more precisely the basis for selecting therapy. The Ann Arbor staging cannot explain the underlying biologic heterogeneity of NHL[13]. Study by Kramer et al. (1998) also revealed that there was no significant correlation between c-MYC expression and disease stage ($p > 0.05$)[14]. However, the different result was obtained from Chang et al. (2000) study who reported that high clinical stage was associated with overexpression of c-MYC ($p < 0.005$)[15].

In addition, a few studies reported that Ann Arbor staging could not determine the overall survival in NHL[16,17]. *C-MYC* gene translocation and rearrangement are more associated with poor prognosis in NHL than clinical staging[11]. Although many studies reported that the poor prognosis is associated with overexpression of c-MYC, but several studies found that the underlying mechanism may be related to other genetic alterations, and the effects of c-MYC overexpression alone were not significantly associated with poor prognosis. A review mentioned that double-expressors of DLBCL (c-MYC and BCL-2 coexpression) were the poor prognostic marker in DLBCL. The advanced stages, high international prognostic index (IPI) score, and relapsed disease were more common in patients of DLBCL with double expression[18].

BAX is a main proapoptotic member of the BCL-2 family proteins that regulates apoptotic function. BAX can be a regulator of apoptosis in both the extrinsic and intrinsic pathways. BAX can suppress the tumor growth and decreased of BAX level is related to chemotherapy resistance[9].

There was no difference of BAX expression with various Ann Arbor stages in B-cell large cell type of NHL in this study. BAX expression is not a major independent prognostic factor in NHL and BAX expression alone cannot be used as a prognostic marker[19]. Study by Gascoyne et al. (1997) found that there was an association between BAX and BCL-2 that was related to prognosis. For example, if the patients had negative expression of BAX and BCL-2, they also had much lower overall survival (OS) when compared to patients who had positive of BAX expression, but the expression of BCL-2 was negative. The interpretation of this results revealed that loss of BAX and BCL-2 expression was an indication of deregulated apoptosis control resulting in more aggressive of tumor growth[20]. The different result was obtained from Yin et al. (2001) study who reported that there was a significant correlation of BAX immunonegative tumors with shorter overall survival[21].

BAX has an important role in the p53-induced apoptotic pathway that can suppress the oncogenic transformation of *c-MYC* and *E1A*. However, upregulation of BAX is not the only protein that determines apoptosis, because there are other proteins such as NOXA and PUMA, which are more commonly correlated with p53-induced apoptosis than BAX protein[22]. The Ann Arbor staging has been used for risk stratification before therapy dan

for therapy selection in NHL. BAX expression and Ann Arbor staging are not related because the staging cannot fully explain the biologic as well as the variation of cellular and molecular factors of the tumor[15].

There was no correlation between c-MYC and BAX expressions ($p > 0.05$). This indicated that the level of c-MYC expression did not affect the BAX expression in various Ann Arbor stages in B-cell large cell type of NHL. Study by Soucie et al. (2001) reported that there was no difference in BAX protein expression detected, either in the presence or absence of c-MYC. This study also revealed that c-MYC expression did not change the BAX expression during growth and apoptosis process[23,24,25,26,27,28,29].

Deregulation of c-MYC causes not only tumor cells proliferation but also apoptosis in partnership with ARF and p53. C-MYC can induce the expression of ARF, which causes apoptosis through the p53 activation, wherein this p53 stimulates BAX activity. However, both of c-MYC and ARF can trigger apoptosis without p53 wherein ARF will directly bind to c-MYC to inhibit hyperproliferation and transformation. ARF is important on c-MYC to stimulate the transcription of target gene, *Egr1*. Egr1 is also important for p53 independent c-MYC-induced apoptosis. The transcriptional induction Egr1 by c-MYC depends on the ability of ARF to alter the c-MYC activity from proliferative to apoptotic protein without p53[24,30,31,32,33,34,35].

CONCLUSION:

There was no difference between c-MYC and BAX expression with various Ann Arbor stages in B-cell large cell type of NHL. This indicated that C-MYC and BAX expression alone could not to be used as parameters to predict the outcome of the B-cell large cell type of NHL via Ann Arbor stages.

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CONFLICTS OF INTEREST:

The authors declare that they have no conflict of interest.

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