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The Ki-67 index in non-Hodgkin's Lymphoma: Role and Prognostic Significance

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Abstract **Background**: Ki67 is a nuclear and nuclear protein antigen present in all proliferating cells during the active part of the cell cycle: G1, S, G2, and mitosis. The aim of study is to evaluate survival based on Ki67 index in NHL patients in the west of Iran for the first time. **Patients and Methods:** Between of 2002 to 2014, fifty-six patients with NHL referred to Our Clinic. We checked age, sex, type of NHL, Ki67 index and survival for them. We divided Ki67 index to two groups: low Ki67 (Ki67<65%) and high Ki67 (Ki67≥65%). **Results**: The mean age at diagnosis for patients was 47.33±166.50 years (range, 13-77 years) that 27 patients (48.2%) had age≤ 50 years and 33 patients (58.9%) were male. Thirty-eight patients (67.9%) had Ki67<60% and 18 patients (32.1%) had Ki67≥65%. The mean Ki67 for Nodal patients was 48.1% and for extra nodal was 54.5%, but there was no significant correlation between them (P=0.360). **Conclusion**: Ki67 in future studies should be divided based on a fix percent until we can have a better result about the role of Ki67 in NHL patients. Also, Ki67 alone can not be a risk factor in NHL patients and other factors such as age, sex and type of NHL can be affective, too.

Keywords: *Ki67 index, overall survival, NHL*

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1. Introduction

The Ki67 antigen was first described by Gerdes & colleagues in the early 1980s, by use of a mouse monoclonal antibody against a nuclear antigen from a Hodgkins lymphoma derived cell line. Immunohistochemical expression of Ki67 antigen in paraffin section called Ki67 proliferative index, represents the active growth fraction of the tumor. As various studies confirmed the correlation of Ki67 index (Figure 1 and Figure 2) with tumor grade and clinical behavior of the tumors, it became the routine part of various tumor workup especially breast cancer and lymphoid neoplasms [1,2].

Ki67 is a nuclear and nucleolar protein antigen present in all proliferating cells during the active part of the cell cycle: G1, S, G2, and mitosis. Its expression is evaluated immunohistochemically by dividing the number of cells that stain positively for Ki67 with the total number of cells in the sample [3]; this is referred to as the proliferation index (PI). In human tissues, Ki67 expression has been found to be highly correlated with the proliferation rate [4], and it may be used to determine the growth fraction of a given human cell population.

The aim of study is to evaluate survival based on Ki67 index in non-Hodgkin's lymphoma (NHL) patients in the west of Iran for the first time.

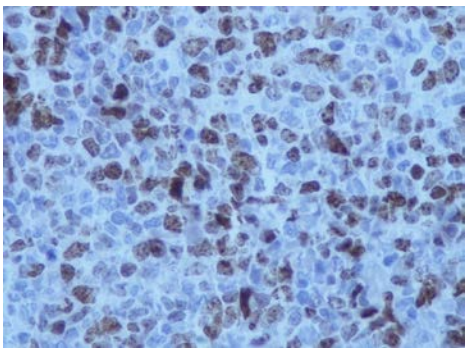

Figure 1. Histopathology image for Ki67 with 50% in cells (×400)

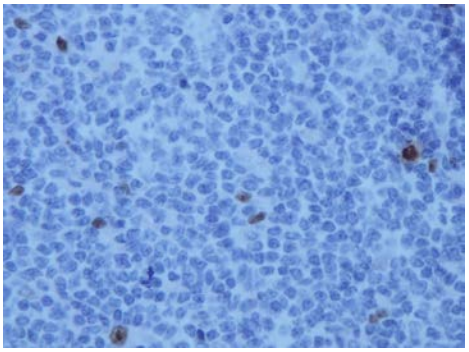

Figure 2. Histopathology image for Ki67 under 5% in cells (×400)

2. Patients and Methods

Between of 2002 to 2014, fifty-six patients with NHL referred to Our Clinic, Kermanshah City, Iran. We checked age, sex, type of NHL, Ki67 index and survival for them.

Once a diagnosis of NHL was made by the hospital pathologist, slides and frozen material were sent for review to a panel of four regional pathologists, experienced in hemato-pathology. Immunohistochemical (IHC) stains using antibodies against CD 20, CD 3, CD 10, CD 5, CD 23, BCL2 and cyclinD1 were done in each case. The cases were diagnosed by morphology on H and E sections and IHC profile according to WHO classification of lymphoid neoplasms by senior histopathologists. We divided Ki67 index to two groups: low Ki67 (Ki67<65%) and high Ki67 (Ki67≥ 65%). The correlation between variables with Ki67 index was done by SPSS software (Chi-square test) and also correlation between Ki67 index with type of NHL was done with T-test. The OS was plotted by GraphPad Prism 5 software.

3. Results

The mean age at diagnosis for patients was 47.33±166.50 years (range, 13-77 years) that 27 patients (48.2%) had age≤ 50 years and 29 patients (51.8%) had age >50 years (Table 1). Of all patients, 33 patients (58.9%) were male and 23 patients (41.1%) were female. Type of NHL for 30 patients (53.6%) was nodal and for 26 patients (46.4%) was extra nodal. We divided Ki67 index to two groups that 38 patients (67.9%) had Ki67<60% and 18 patients (32.1%) had Ki67≥65%.

Table 1. the characteristics for all patients (n=56)

Variables	n(%)	Mean±SD	Range
Age(year)			
Age group(year)			
≤50	27(48.2)		
>50	29(51.8)		
Sex			
Male	33(58.9)		
Female	23(41.1)	47.33±16.50	13-77
Type of NHL			
Nodal	30(53.6)		
Extra nodal	26(46.4)		
Ki67(%)			
<65*	38(67.9)		
≥65**	18(32.1)		

*Low Ki67 **High Ki67

Table 2. the characteristics for all patients based on Ki67 index (n=56)

Variables	Low Ki67	High Ki67	P-value
Age			
≤50	15	12	0.053
>50	23	6	
Sex			
Male	21	12	0.304
Female	17	6	
Type of NHL			
Nodal	21	9	0.466
Extra nodal	17	9	

We compared age, sex and type of NHL with Ki67 index and correlation between them (Table 2). There was no significant correlation between variables with Ki67 index (P>0.05). The mean Ki67 for Nodal patients was 48.1% and for extranodal was 54.5%, but there was no significant correlation between them (P=0.360).

The 3-year, 5-year and 10-year OS for all patients has been written in Figure 3. There was no significant correlation between low Ki67 and high Ki67 for 3-year, 5-year and 10-year periods (P>0.05).

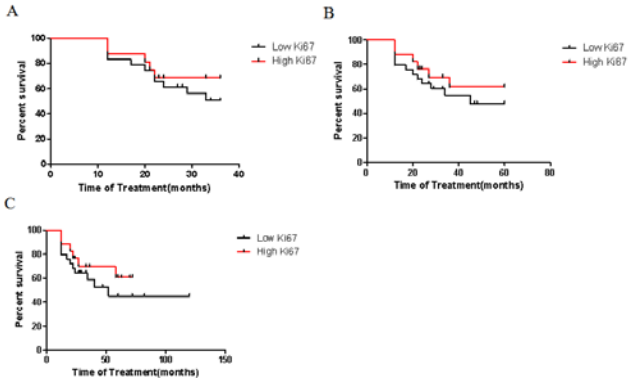

Figure 3. The overall survival for all patients based on Ki67 index (A) 3-year (B) 5-year (C) 10-year

4. Discussion

Ki67 is a nuclear antigen expressed by dividing cells. Thus, the percentage of Ki67-positive cells reflects the proportion of actively proliferating tumor cells [5]. The role of Ki67 index as a prognostic and predictive factor is extensively evaluated in several studies in NHL patients [6,7]. In a study, Ki67 for NHL patients divided to >70% (high) and ≤70% (low) that 3-year survival was 55.9% ± 6% in the patients with a high index (mean overall survival 49.3% ± 3.9 months, median 78 months) and 75% ± 5.6% in those with a low index (mean overall survival 77.9 ± 4.7, median not reached, P =0.015) [8]. In other study, Ki67 for NHL patients divided to <65% (low) and ≥65% (high) that in the univariate analysis, the group with high Ki-67 expression had a shorter OS (P = 0.021) [9]. A study by the Nordic Lymphoma Group showed that the expression of Ki-67 was not associated with survival difference in patients with diffuse large B-cell lymphoma [10]. Ninety-one patients could be analysed for survival and those with low grade lymphoma (n = 38) who had a relatively high Ki67 index (greater than 5 per cent) had a worse survival than those with an index of less than 5 per cent (P<0.05) [11]. In our study, NHL patients divided to <65% (low) and ≥65% (high) that there was no significant correlation between Ki67 index with the OS. In our study, the OS for High Ki67 was higher than low Ki67 that probably, race (Kurdish) and type of treatment in patients was affective on Ki67 that for a good result, we in future studies will discussed about type of treatmen. Although the reason for these inconsistent results regarding the prognostic significance of Ki67 expression in non-Hodgkin's lymphoma remains unclear, the following might be possible explanations. A different definition for high Ki67 expression might be related to different results. The arbitrarily defined various cut-offs from 20% to 80% were used for high Ki67 expression to dichotomize their study populations into high and low Ki67 expression [10,12,13]. Therefore, Ki67 in future studies should be divided based on a fix percent until we can have a better result about the role of Ki67 in NHL patients. Researchers

have established prognostic factors of NHL: patient-related (age, performance status, and B symptoms) and disease-related (number of nodal and extranodal sites, tumor stage, and tumor size), and biological measures (serum hemoglobin, b2 microglobulin, and lactate dehydrogenase) [14]. A study reported that there is a correlation between Ki67 with age (<60 years vs. >60 years) and the OS [8]. In this study, there is no significant correlation between age (≤50 years vs. >50 years, sex and type of NHL with Ki67 index. Also, a study showed that there is no correlation between age with Ki67 [9].

5. Conclusion

Ki67 in future studies should be divided based on a fix percent until we can have a better result about the role of Ki67 in NHL patients. Also, Ki67 alone can not be a risk factor in NHL patients and other factors such as age, sex and type of NHL can be affective, too.

References

[1] Haroon S, Hashmi AA, Khurshid A, Kanpurwala MA, et al, Mujtuba S, Malik B. Ki67 index in breast cancer: correlation with other prognostic markers and potential in Pakistani patients. Asian Pac J Cancer Prev. 2013. 14 (7): 4353-8.

[2] Niikura N, Iwamoto T, Masuda S, Kumaki N, Xiaoyan T, Shirane M, et al. Immunohistochemical Ki67 labeling index has similar proliferation predictive power to various genesignatures in breast cancer. Cancer Sci. 2012. 103 (8): 1508-12.

[3] Brown DC, Gatter KC. Ki67 protein: the immaculate deception? Histopathology. 2002. 40 (1): 2-11.

[4] Endl E, Gerdes J. The Ki-67 protein: fascinating forms and an unknown function. Exp Cell Res. 2000. 257 (2): 231-7.

[5] Went P, Agostinelli C, Gallamini A, Piccaluga PP, Ascani S, Sabattini E, Bacci F, Falini B, Motta T, Paulli M, Artusi T, Piccioli M, Zinzani PL, Pileri SA. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol. 2006. 24 (16): 2472-9. Epub 2006 Apr 24.

[6] Hadzi-Pecova L, Petrusevska G, Stojanovic A. Non-Hodgkin's lymphomas: immunologic prognostic studies. Prilozi. 2007. 28 (1): 39-55.

[7] Gaudio F, Giordano A, Perrone T, Pastore D, Curci P, Delia M, et al. High Ki67 index and bulky disease remain significant adverse prognostic factors in patients with diffuse large B cell lymphoma before and after the introduction of rituximab. Acta Haematol. 2011; 126 (1): 44-51.

[8] Broyde A, Boycov O, Strenov Y, Okon E, Shpilberg O, Bairey O. Role and prognostic significance of the Ki-67 index in non-Hodgkin's lymphoma. Am J Hematol. 2009. 84 (6): 338-43.

[9] Kim SJ, Kim BS, Choi CW, Choi J, Kim I, Lee YH, et al. Ki-67 expression is predictive of prognosis in patients with stage I/II extranodal NK/T-cell lymphoma, nasal type. Ann Oncol. 2007. 18 (8): 1382-7.

[10] Jerkeman M, Anderson H, Dictor M, Kvaløy S, Akerman M, Cavallin-Ståhl E, et al Assessment of biological prognostic factors provides clinically relevant information in patients with diffuse large B-cell lymphoma--a Nordic Lymphoma Group study. Ann Hematol. 2004. 83 (7): 414-9. Epub 2004 Apr 14.

[11] Hall PA, Richards MA, Gregory WM, d'Ardenne AJ, Lister TA, Stansfeld AG. The prognostic value of Ki67 immunostaining in non-Hodgkin's lymphoma. J Pathol. 1988. 154 (3): 223-35.

[12] Went P, Agostinelli C, Gallamini A, Piccaluga PP, Ascani S, Sabattini E, et al. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol. 2006. 24 (16): 2472-9. Epub 2006 Apr 24.

[13] Miller TP, Grogan TM, Dahlberg S, Spier CM, Braziel RM, Banks PM, et al. Prognostic significance of the Ki-67-associated proliferative antigen in aggressive non-Hodgkin's lymphomas: a prospective Southwest Oncology Group trial. Blood. 1994. 83 (6): 1460-6.

[14] Gribben J, Steward A, Casce L. Clinical manifestations, staging, and treatment of non-Hodgkin lymphoma. In: Hoffman R, Benz E, Shattil S, et al., editors. Hematology: Basic Principles & Practice. Philadelphia: Elsevier; 2005. pp 1397-1419.