

Effects of CD4 Level on Abnormal Cervical Cytology in HAART-naïve HIV-seropositive Women

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ABSTRACT

Aim: To study the effects of cluster of differentiation 4 (CD4) level on abnormal cervical cytology in human immunodeficiency virus (HIV)-infected women who have not received highly active antiretroviral therapy (HAART).

Materials and methods: Retrospective cross-sectional study was carried at Hatyai Hospital from October 1, 2010 to June 30, 2016. Medical records of 270 HIV-infected women who have not received HAART and have been screened for cervical cancer with Pap smear were reviewed. The CD4 level has been evaluated in all patients. Participants were divided into two groups: 135 patients with CD4 < 200 cells/μL (low CD4 group) and 135 patients with CD4 at least 200 cells/μL (high CD4 group). Statistical analysis was performed.

Results: The prevalence of abnormal cervical cytology in HIV-infected women who have not received HAART was 25.9%. There was difference in prevalence of abnormal cervical cytology between low and high CD4 groups (37.8 vs 17.0%) with statistical significance ($p = 0.001$). Odds ratio was 2.60 (95% confidence interval: 1.47–4.61).

Conclusion: The low CD4 level (CD4 < 200 cells/μL) in HIV-infected women who did not receive HAART increased risk of abnormal cytology of 2.6 folds, compared with high CD4 level (CD4 at least 200 cells/μL). The prevalence of abnormal cervical cytology in HIV-infected women who have not received HAART was 25.9%.

Clinical significance: Human immunodeficiency virus infection is the significant risk factor of cervical cancer. The authors evaluated the effects of CD4 level on abnormal cervical cytology in women who have not received HAART.

Keywords: Abnormal cervical cytology, Cluster of differentiation 4 level, Highly active antiretroviral therapy-naïve human immunodeficiency virus-seropositive women.

How to cite this article: Neamtan S, Noothong S, Pulsawat A. Effects of CD4 Level on Abnormal Cervical Cytology in HAART-naïve HIV-seropositive Women. *J South Asian Feder Obst Gynae* 2018;10(2):84-87.

Source of support: Nil

Conflict of interest: None

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Date of received: 15 March 2018

Date of acceptance: 20 April 2018

Date of publication: July 2018

INTRODUCTION

Cervical cancer is in the fourth rank of cancer in females following breast cancer, lung cancer, and colorectal cancer.¹ There are 520,000 new patients worldwide each year. In Thailand, cervical cancer is the second most common cancer following breast cancer.² Every year, there are 8,100 new patients and 4,500 patients die from the disease.³ According to the data from Hatyai Hospital, the numbers of patients increase every year. From 2011 to 2015, there were 570 patients with cervical cancer and 1,237 patients were diagnosed with cervical precancerous lesion.

Cervical cancer takes several years to develop from cervical precancerous lesion to invasive cancer. However, cervical cancer can be screened.⁴ Therefore, early diagnosis and treatment from cervical precancerous lesion would help to reduce the numbers of cervical cancer patients, particularly high-risk patients.

Human immunodeficiency virus-infected patients are at risk of infection and cancers because of low immunity. Cervical carcinoma is one of the diseases with high prevalence in HIV patients. Its prevalence is about 20%.⁵ The CD4 level affects the severity of cervical cancer, especially in HIV-infected patients because the immune deficiency increases the possibility of human papillomavirus infection and persistent infection.

There was inconsistency between the effects of CD4 level and abnormal cervical cytology. Cardillo et al⁶ found statistically significant difference between mean CD4 level (246 vs 378 cells/μL) and abnormal cervical cytology.

However, Enebe et al⁷ studied about the relationship between CD4 level and prevalence of abnormal cervical cytology in HAART experienced HIV-positive women. They found that the prevalence of abnormal cervical cytology in low CD4 group (CD4 < 200 cells/μL) was 10.2% and it was 5.7% in high CD4 group (CD4 ≥ 200 cells/μL), but no statistical significance.

The inconsistency between the effects of CD4 level and abnormal cervical cytology were observed in data from Thailand, too. The prevalence of abnormal cervical

cytology in HIV-positive women was about 13 to 20% in this country.⁸⁻¹⁰ Chalermchokcharoenkit et al⁸ studied in postpartum HIV-positive women, reported higher prevalence of abnormal cervical cytology in low CD4 group (CD4 < 200 cells/ μ L) compared with high CD4 group (CD4 \geq 200 cells/ μ L) with statistical significance. Sirivongrangson et al⁹ also reported higher prevalence of abnormal cervical cytology in HIV-positive women, but no statistical significance.

Therefore, the primary objective of this study was to determine the effects of high and low CD4 level on abnormal cervical cytology in HIV-infected women who have not received HAART. The secondary objective was to find the prevalence of abnormal cervical cytology in HIV-infected women who have not received HAART.

MATERIALS AND METHODS

This retrospective cross-sectional study was approved by the Institutional Review Board and performed at Department of Obstetrics and Gynecology, Hatyai Hospital. Medical records of HIV-infected women who have not received HAART (all women were screened for cervix cancer by Pap test) between October 1, 2010 and June 30, 2016 were reviewed. Patients were excluded with the following conditions: (a) Previously diagnosed with preinvasive cervical lesion or cervical carcinoma, (b) previously received pelvic radiation, cervical surgery, or total hysterectomy, (c) pregnant women, and (d) incomplete medical record.

Definitions of following variables are: (a) CD4 means CD4 lymphocyte. (b) HIV-infected women are HIV-positive women diagnosed by the Department of Disease Control, Ministry of Public Health, Thailand criteria.⁵ (c) Contraception means current contraception method. Abnormal cervical cytology was reported based on 2001 Bethesda system.¹¹

Statistical analyses were performed using STATA version 13.0 (Stata Corp, College Station, Texas). The clinical data of the patients were analyzed by descriptive statistics. Continuous data were presented with mean \pm standard deviation, median (1st, 3rd quartile). Data with normal distribution were analyzed by unpaired two-tailed t-test. Data with non-normal distribution were analyzed by Mann-Whitney U test. Discrete data were analyzed by Chi-square test, Fisher's exact test and odds ratio (95% confidence interval). For all analyses, p-value < 0.05 was considered statistically significant.

RESULTS

The authors gathered information of 270 HIV-infected women who have not received HAART and had been screened for cervical cancer with Pap smear. A total of

135 patients had low CD4 level (CD4 < 200 cells/ μ L) and 135 patients had high CD4 level (CD4 \geq 200 cells/ μ L). Most patients were 35 years or older (21–62 years old), accounted for 58.5% in the group with low CD4 level and 68.9% in the group with high CD4 level.

The correlation between CD4 level and patient characteristics: 24 patients with low CD4 level had two or more lifetime sexual partners, accounting for 17.8%. On the contrary, only four patients with high CD4 level had two or more lifetime sexual partners, accounting for 3% (p = 0.001). Other factors, including oral contraceptive use, smoking behavior, parity and sexually transmitted disease, were not statistically significant. Detailed result of patient characteristics is shown in Table 1.

The median CD4 level in the low CD4 group was 60 cells/ μ L (25th percentile: 27 cells/ μ L, 75th percentile: 119 cells/ μ L), while median CD4 level in the high CD4 group was 342 cells/ μ L (25th percentile: 263 cells/ μ L, 75th percentile: 498 cells/ μ L). The difference of CD4 level between two groups was statistically significant (p < 0.001).

Of 270 HIV-infected women who have not received HAART, 70 patients had abnormal cervical cytology. Therefore, the prevalence of abnormal cervical cytology in HIV-infected women who have not received HAART was 25.9%. For the low CD4 group, abnormal cervical cytology was found in 47 patients. Thus, the prevalence of abnormal cervical cytology in this group was 37.8%, although 23 patients with abnormal cervical cytology were found in the high CD4 group. Therefore, the prevalence of abnormal cervical cytology in the high CD4 group was 17.0%. The prevalence of abnormal cervical cytology in both groups was the difference with statistical significance (p = 0.001). Odds ratio was 2.60 (95% confidence interval: 1.47–4.61).

The degrees of abnormal cervical cytology according to the 2001 Bethesda System¹¹ are shown in Table 2. None of the participants had atypical glandular cells, not otherwise specified (AGC-NOS), atypical glandular cells, favor neoplastic (AGC-FN), endocervical adenocarcinoma in situ (AIS), or adenocarcinoma. Furthermore, from data analysis of the low CD4 group compared with the high CD4 group, there was no significant difference in prevalence of patients with various degrees of abnormal cervical cytology.

DISCUSSION

Cervical cancer is the major public health problem in Thailand, particularly among HIV-infected patients. Human immunodeficiency virus infection reduces the immune system's ability to get rid of infections, causing low immunity that results in susceptibility to infection and causes cervical cancer intensified.

Table 1: Patient characteristics

Characteristics	CD4 < 200 cells/ μ L (n = 135)	CD4 \geq 200 cells/ μ L (n = 135)	p-value
Age (years)			
<35	56 (41.5)	42 (31.1)	0.076 ^a
\geq 35	79 (58.5)	93 (68.9)	
CD4 level (cells/ μ L)	60 (27.119)	342 (263.498)	<0.001 ^{b,*}
Oral contraceptive use	6 (4.4)	5 (3.7)	0.758 ^a
Smoking			
Yes	5 (3.7)	5 (3.7)	1.000 ^a
No	130 (96.3)	130 (96.3)	
Lifetime sexual partners			
\leq 2	111 (82.2)	131 (3.0)	<0.001 ^{c,*}
>2	24 (17.8)	4 (3.0)	
Parity			
\leq 4	132 (97.8)	133 (98.5)	1.000 ^c
>4	3 (2.2)	2 (1.5)	
Sexually transmitted disease			
Syphilis	0 (0)	3 (2.2)	0.247 ^c
Herpes simplex	12 (8.9)	11 (8.1)	0.827 ^a
Hepatitis B	7 (5.2)	6 (4.4)	0.776 ^a
Hepatitis C	4 (3)	2 (1.5)	0.684 ^c

Values are given as median (1st, 3rd quartile), or number (%). ^aChi-square; ^bMann–Whitney U test; ^cFisher's exact test; *Significant at $p < 0.05$

Table 2: Abnormal cervical cytology by high and low white blood cell CD4 level

	CD4 < 200 cells/ μ L (n = 135)	CD4 \geq 200 cells/ μ L (n = 135)	Odds ratio (95% confidence interval)	p-value
Abnormal cervical cytology	47 (37.8)	23 (17.0)	2.60 (1.47–4.61)	0.001 ^{a,*}
ASC-US	7 (5.2)	4 (3.0)	1.79 (0.51–6.27)	0.540 ^b
LSIL	19 (14.1)	9 (6.7)	2.29 (1.00–5.53)	0.050 ^a
ASC-H	2 (1.5)	0 (0)	–	0.498 ^b
HSIL	17 (12.6)	8 (5.9)	2.29 (0.95–5.50)	0.059 ^b
SCCA	1 (0.7)	1 (0.7)	1.00 (0.06–16.15)	1.000 ^b
AGC	1 (0.7)	1 (0.7)	1.00 (0.06–16.15)	1.000 ^b

Values are given as number (%). ^aChi-square test; ^bFisher's exact test; *Significant at $p < 0.05$; ASC-US: Atypical squamous cells of undetermined significance; LSIL: Low-grade squamous intraepithelial lesion; ASC-H: Atypical squamous cells cannot exclude HSIL; HSIL: High-grade squamous intraepithelial lesion; SCCA: Squamous cell carcinoma; AGC: Atypical glandular cells

There was inconsistency between effects of CD4 level on abnormal cervical cytology. This research divided HIV-infected women into two groups based on CD4 level: high CD4 group (CD4 \geq 200 cells/ μ L) and low CD4 group (CD4 < 200 cells/ μ L). The research focused on the HIV-infected women who have not received HAART. The patients' characteristics showed that two or more lifetime sexual partners are associated with low CD4 level with statistical significance. It can be assumed that having more sexual partners provides more opportunity to be infected with HIV in terms of both viral load and viral strain, causing worse immunity than women with fewer sexual partners. This finding was consistent with the study of Getinet et al.¹² Other factors, such as age, smoking behavior, oral contraceptive use, parity, and sexually transmitted disease had no significant difference between high and low CD4 groups.

The prevalence of abnormal cervical cytology in HIV-infected women who have not received HAART was 25.9% in this study. This was similar to the previous studies that reported about 20 to 27%.^{9,13,14} However, Chalermchockcharoenkit et al⁸ reported the prevalence of abnormal cervical cytology at 13.3%. Further study was conducted in 2011 and found that the prevalence of abnormal cervical cytology in HIV-infected women was 15.4%.¹⁰ Inconsistent of the results may be from the participants of the present study were HAART naïve, while most participants in Chalermchockcharoenkit study had received HAART. Therefore, there is higher possibility of low immune patient in the present study, causing more chance of developing abnormal cervical cytology.

Considering by high and low CD4 level, the prevalence of abnormal cervical cytology in the low CD4 group was 37.8%, which was 2.6 times higher than those with high

CD4 group whose prevalence of abnormal cervical cytology was 17.0%. This finding was in line with the study of Chalermchokcharoenkit et al.⁸ They illustrated that the prevalence of abnormal cervical cytology in HIV-infected women who had CD4 level <200 cells/ μ L was 21.2%, whereas the prevalence of abnormal cervical cytology in the patients who had CD4 level \geq 200 cells/ μ L was 12.2%. The difference of prevalence of abnormal cervical cytology was statistically significant. The divergence of prevalence in the two studies may be caused by different patient population. Most participants in Chalermchokcharoenkit study have received HAART. Enebe et al.⁷ found that the prevalence of abnormal cervical cytology in HIV-infected women who had low CD4 (CD4 <200 cells/ μ L) was 10.2% while those who had high CD4 (CD4 \geq 200 cells/ μ L) was 5.7%. Moreover, the low CD4 group had higher prevalence of abnormal cervical cytology than the high CD4 group. However, the difference had no statistical significance.

This present study had sufficient sample size to conclude that CD4 level less than 200 cells/ μ L was the risk factor of abnormal cervical cytology, compared with CD4 200 cells/ μ L or over, with 2.6 fold risk. Moreover, this study included only HAART-naïve patient. Thus, it could be clearly concluded that CD4 level affected development of abnormal cervical cytology in HIV-infected women. From this finding, the physician should determine CD4 level in HIV patients at first diagnosis because severity of CD4 level is associated with severity of abnormal cervical cytology. Moreover, the follow-up interval of patients with low CD4 level should be shorter compared with patients with high CD4 level or normal population.

However, there was no significant difference in prevalence of various degrees of abnormal cervical cytology, according to the 2001 Bethesda System. However, because the sample size of each subgroup was small, additional study of each subgroup and association with CD4 level would be necessary. Furthermore, this research was a retrospective study, so some data might not be complete, which is the limitation of this study.

CONCLUSION

The low CD4 level (CD4 <200 cells/ μ L) in HIV-infected women who have not received HAART increased the risk of abnormal cytology 2.6 folds, compared with high CD4 level (CD4 \geq 200 cells/ μ L). The prevalence of abnormal cervical cytology in HIV-infected women who had not received HAART was 25.9%.

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