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Original Article

Non-Hodgkin's Lymphoma in Patients With Human Immunodeficiency Virus Infection in Taiwan

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BACKGROUND/PURPOSE: Non-Hodgkin's lymphoma (NHL) is the second most common acquired immunodeficiency syndrome-defining malignancy with a high mortality rate. This study aimed to describe changes in the incidence and clinical characteristics of NHL in human immunodeficiency virus (HIV)-infected patients in a referral hospital for HIV care.

METHODS: The medical records of HIV-infected patients diagnosed with NHL between June 1994 and December 2006 were retrospectively reviewed. Risk stratification of each patient was evaluated using the International Prognostic Index (IPI). Case patients were followed at least for 2 years to assess the 2-year survival rates.

RESULTS: During the 12-year period, 38 HIV-infected patients were diagnosed with NHL. Their median cluster of differentiation 4 count was 82 cells/μL (range, 2–477 cells/μL) at diagnosis. Before the introduction of highly active antiretroviral therapy (HAART) in April 1997, 9/175 HIV-infected patients (5.1%) developed NHL compared with 29/1,386 patients (2.1%) in the HAART era ($p < 0.05$). Although the 2-year survival rate did not differ significantly between patients diagnosed in the pre-HAART era (22.2%) and those diagnosed in the HAART era (24.1%), patients receiving HAART for more than 6 months had better survival rates ($p < 0.05$). A low IPI score was a good prognostic factor predictive of a patient's outcome.

CONCLUSION: The incidence of NHL in HIV-infected patients declined significantly in the HAART era. Despite the introduction of HAART, the short-term survival of the patients with NHL remained poor. The IPI was a good predictor for survival.

KEYWORDS: AIDS, HIV, non-Hodgkin's lymphoma, Taiwan

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Introduction

Kaposi's sarcoma and non-Hodgkin's lymphoma (NHL) are the most common malignancies in human immunodeficiency virus (HIV)-infected patients.[1] After recognition of acquired immunodeficiency syndrome (AIDS) and HIV infection, it has been noted that the incidence of both NHL and Hodgkin's lymphoma is much higher in HIV-infected patients than in the general population.[2–4] In a review of the cancer registries of 11 regions in the United States (Surveillance Epidemiology and End Results Program), the incidence of NHL increased from 10.4/100,000 in 1973 (before the onset of the AIDS epidemic) to 21.1/100,000 in 1995.[5] Therefore, NHL has been defined as an AIDS-defining illnesses, in addition to primary central nervous system (CNS) lymphoma, since 1985.[6]

The risk factors for HIV-associated NHL are not well understood, but the absolute risk increases with age and is higher in men and in whites.[7] Although the incidence of HIV-associated NHL has decreased and the survival of the patients with HIV-associated NHL has been improved after highly active antiretroviral therapy (HAART) was introduced, NHL is still a prominent malignancy in patients with AIDS.[8–12]

In Taiwan, the mortality of HIV-infected patients has declined significantly in the HAART era, and non-AIDS-related conditions are now increasingly recognized as causes of death.[13] However, there are few reports on the characteristics of NHL in HIV-infected patients in Taiwan. In this study, we aimed to describe the change in the incidence and clinical characteristics of NHL in patients with HIV infection enrolled in an observational study at a referral hospital for HIV care in Taiwan.

Methods

Ethics

This study was approved by the Institutional Review Board of the National Taiwan University Hospital and the need for informed consent was waived.

Study population

A total of 1,561 non-hemophiliac HIV-infected persons aged 15 years or older, who received medical care between June 1994 and December 2006, were enrolled in an prospective observational study at the National Taiwan University Hospital, the largest referral hospital for inpatient and outpatient care in Taiwan.[14] The date of enrollment was defined as the date of the first visit at which the patient sought HIV care at the hospital. A computerized case report form was used to record patient demographics, risk factors for HIV-infection, cluster of differentiation 4 (CD4) and CD8 lymphocyte counts, plasma HIV RNA load, HIV-related opportunistic illnesses (including opportunistic infections and malignancies), prescribed antiretroviral therapy (including HAART), therapy for malignancy and outcomes. Patients were divided into two groups based on the date of enrollment: from June 1994 to March 31, 1997 (pre-HAART) and from April 1, 1997 to December 31, 2006 (post-HAART). The study ended on December 31, 2008.

Diagnostic investigations

During the 12-year study period, all the patients received stepwise investigations described previously as routine clinical care practices to identify the etiology of any presenting symptoms and signs.[15] For patients who presented with lymphadenopathy or mucocutaneous lesions, biopsy was performed if necessary. For visceral lesions, which remained unknown after serial non-invasive diagnostic tests, sonography, computed tomography or endoscopy-guided aspiration and biopsy (for those lesions that were accessible) were performed. Also, microbial cultures including cultures for bacteria, fungi, mycobacteria, and viruses were performed (especially for febrile patients).

Definitions

NHL was defined as definite if the lesions were diagnosed by histopathology. Probable cases were defined as those lesions with characteristic appearance, plus compatible clinical findings and exclusion of other possible infectious diseases, and a favorable response to specific therapy for NHL, e.g. systemic chemotherapy or radiotherapy.

Each patient was evaluated using the International Prognostic Index (IPI), which was established in 1993 by the International Non-Hodgkin's Lymphoma Prognostic Project. The IPI criteria are: (1) age > 60 years; (2) serum lactate dehydrogenase concentration above normal; (3) Eastern Cooperative Oncology Group Performance Status Scale ≥ 2; (4) Ann Arbor stage III or IV; and

(5) more than one extra-nodal disease site.[16] Each factor counts as one score and the risk is stratified according to the sum of scores: low risk = 0–1; low-intermediate risk = 2; high-intermediate risk = 3; high risk = 4–5. The stratified risk group was associated with different 5-year survival rates.

Statistical analysis

All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared by Fisher's exact test or χ^2 test. Non-categorical variables were compared using the Mann-Whitney *U* test. All comparisons were two-tailed and a p value < 0.05 was considered statistically significant.

Results

From June 1994 to December 2006, 1,561 HIV-infected patients were enrolled. Their median CD4 count at baseline was 110 cells/μL and 56.1% had a baseline CD4 count < 200 cells/μL. The major route of HIV transmission was sexual contact. Malignancy was documented in 7.8% (121/1,561) of the enrolled patients. Kaposi's sarcoma was the most common (67/1,561; 4.3%) followed by NHL (38/1,561; 2.4%). The 38 patients with NHL comprised the study population in the present study, and their demographics and clinical characteristics are shown in Table 1.

Most of the patients were heterosexuals (55.3%). At the time of NHL diagnosis, the median age of the patients was 39.9 years (range, 22.5–66.9 years), 71.1% (27/38) had a CD4 cell count < 200 cells/μL, and 76.3% (29/38) were naïve to antiretroviral therapy. The median CD4 count and plasma HIV RNA load were 82 cells/μL (range, 2–477 cells/μL) and 5.32 $\log_{10}$ copies/mL (range, 1.70–5.88 $\log_{10}$ copies/mL), respectively (Table 1). Five patients (13.2%) also had other concurrent malignancies, including Kaposi's sarcoma (4 patients) and hepatocellular carcinoma (1 patient).

The diagnosis was definite in 35 patients (92.1%) and probable in three patients (7.9%). All three probable cases were primary CNS lymphomas. The most common histopathology of NHL was diffuse large B cell lymphoma (57.9%), followed by Burkitt's lymphoma (18.4%), and primary CNS lymphoma (13.2%; Table 1). Nearly 85% of NHL cases presented with extra-nodal involvement. In those patients, the CNS was the most commonly involved extra-nodal site (pre-HAART era, 33.3%; HAART era, 51.7%). Visceral organ involvement was seen in about 20% of patients (pre-HAART era, 22.2%; HAART era, 20.7%), most commonly involving the gastrointestinal tract.

Table 1. Demographics of human immunodeficiency virus-infected patients with non-Hodgkin lymphoma (n = 38)

Baseline data	
Sex, male	35 (92.1)
HIV risk factor	
MSM	15 (39.5)
Heterosexual	21 (55.3)
Others	2 (5.2)
Data at enrollment of cohort	
CD4 count (cells/uL)	43 (2–571)
CD8 count (cells/uL)	580 (56–2,957)
PVL ($\log_{10}$/mL)	5.56 (2.60–5.87)
Data at diagnosis of HIV-associated lymphoma	
Definite cases	35 (92.1)
Probable cases	3 (7.9)
Extra-nodal involvement	33 (84.6)
Concurrent opportunistic infection	21 (55.3)
Concurrent malignancy	5 (13.2)
Age (yr)	39.9 (22.5–66.9)
Antiretroviral-naïve	29 (76.3)
Prior AIDS	29 (76.3)
CD4 count (cells/μL)	82 (2–477)
PVL ($\log_{10}$/mL)	5.32 (1.70–5.88)
Episodes categorized by CD4 count	
< 200 cells/μL	27 (71.0)
200–350 cells/μL	6 (15.8)
> 350 cells/μL	5 (13.2)
Outcome	
2-year survival	9 (23.7)
Histopathology	
Burkitt's lymphoma	7 (18.4)
Primary CNS lymphoma	5 (13.2)
DLBCL	22 (57.9)
Others	4 (10.5)

MSM = Men who have sex with men; CD4 = cluster of differentiation; PVL = plasma HIV RNA load; HIV = human immunodeficiency virus; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma.

Table 2. Incidence rate and other data at diagnosis of human immunodeficiency virus-associated non-Hodgkin's lymphoma according to treatment era[a]

	Pre-HAART era ($n=9$)	HAART era ($n=29$)	p
Proportion of HIV-associated lymphoma (%)	5.1	2.1	<0.05
MSM	1 (11.1)	14 (48.2)	0.06
CD4 count (cells/μL)	97 (3–477)	82 (2–453)	0.83
PVL (log_{10}/mL)	–	5.31 (1.70–5.88)	–
Previous AIDS	7 (77.8)	22 (75.9)	1.00
Antiretroviral-naïve	6 (66.7)	23 (79.3)	0.66
NHL as presenting disease	5 (55.6)	14 (48.3)	1.00
Concurrent opportunistic infection	4 (44.4)	17 (58.6)	0.70
Concurrent malignancy	2 (22.2)	3 (10.3)	0.57
Stage III/IV disease	7 (77.8)	23 (79.3)	1.00
2-year survival	2 (22.2)	7 (24.1)	1.00

[a]Data presented as %, *n* (%) or median (range). MSM = Men who have sex with men; HIV = human immunodeficiency virus; CD4 = cluster of differentiation 4; PVL = plasma HIV RNA load; AIDS = acute immunodeficiency diseases; NHL = non-Hodgkin's lymphoma.

The crude incidence of NHL declined significantly after the introduction of HAART; A total of 9/175 patients (5.1%) developed NHL in the pre-HAART era compared with 29/1,386 patients (2.1%) in the HAART era ($p<0.05$; Table 2). Patients in the HAART era were more likely to be homosexual males (48.2%) than those in the pre-HAART era (11.1%; $p=0.06$). There were no significant differences in CD4 cell counts, prior AIDS status, being naïve to antiretroviral therapy, concurrent opportunistic infections or malignancy, and stage III/IV disease between patients enrolled in the pre-HAART and HAART eras.

Despite the introduction of HAART and improving chemotherapeutic regimens for NHL, 2-year cumulative survival remained poor: 22.2% in the pre-HAART and 24.1% in the HAART era ($p=0.99$; Table 2). Figure 1 shows the Kaplan-Meier survival curve for 2-year survival in the pre-HAART and post-HAART eras. Nearly 40% of the patients died before receiving chemotherapy (44.4% in the pre-HAART era; 37.9% in the post-HAART era). Figure 2 shows 2-year Kaplan-Meier survival curves for patients given HAART for more than 6 months and for those given HAART for less than 6 months. Patients given HAART for more than 6 months had a better survival rate (log-rank test, $p=0.001$).

A low IPI score was associated with better survival ($p<0.05$; Table 3). Other factors that tended to be associated with improved outcome, but were not statistically significant due to the small sample size, included CD4 count > 200 cells/μL, initiation time of HAART, HAART combined with chemotherapy or radiotherapy, stage III/IV disease, and a lower lactate dehydrogenase level (Table 3). Exclusion of the three probable cases of primary CNS lymphoma did not alter the results.

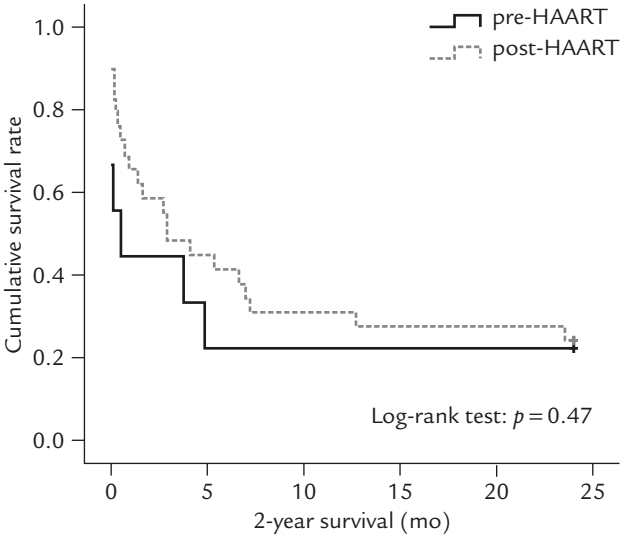

Figure 1. Kaplan-Meier survival plot showing 2-year cumulative survival rates in the pre-highly active antiretroviral therapy (from June 1994 to March 1997) and highly active antiretroviral therapy eras (from April 1997 to December 2006). HAART = Highly active antiretroviral therapy.

Of the nine patients with 2-year survival after the initial diagnosis of NHL, only one was lost to follow-up 30 months later. The remaining eight patients received regular follow-up at clinics and showed no evidence of recurrence.

Discussion

In this study, we found that NHL remains an important HIV-associated malignancy (38/121; 31.4%), though it was not a common AIDS-defined illness (38/1,561; 2.4%). Similar to other opportunistic illnesses,[17] the proportion of our patients diagnosed with NHL declined significantly from 5.1% in the pre-HAART era to 2.1% in the HAART era, which can be attributed to the enrollment of patients during the earlier stages of HIV infection and to the introduction of HAART. However, NHL and other opportunistic illnesses continue to occur in HIV-infected patients with depleted CD4 cell counts. Table 2 shows that more than 70% of patients in both the pre-HAART (77.8%) and HAART eras (75.9%) also had AIDS, or had been diagnosed with AIDS before NHL. Also, a high proportion of patients either had concurrent opportunistic infections (44.4% and 58.6% in the pre-HAART and post-HAART eras, respectively) or were naïve to antiretroviral therapy before NHL diagnosis (66.7% and 79.3% in the pre-HAART and post-HAART eras, respectively). These findings suggest that the importance of early diagnosis of HIV infection, and the continued improvement and promotion of access to HIV testing and care (including HAART) cannot be overemphasized.[17–19]

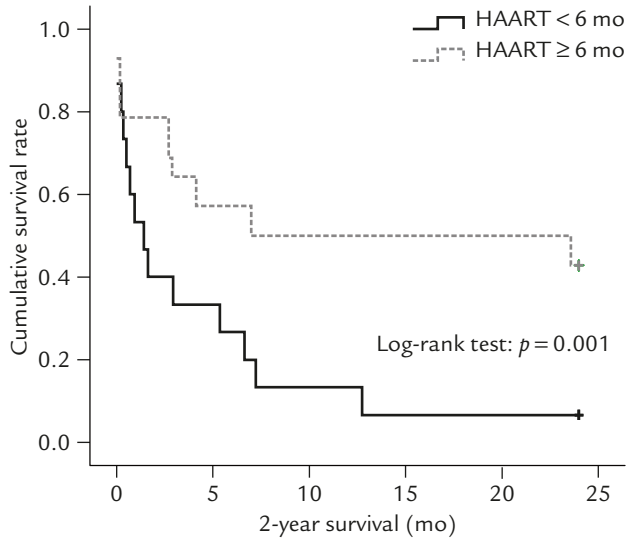

Figure 2. Kaplan-Meier survival plot showing 2-year cumulative survival rates of patients given highly active antiretroviral therapy for ≥6 months or <6 months in the HAART era. HAART=Highly active antiretroviral therapy.

Although the incidence of HIV-associated NHL declines, characteristics such as stage at presentation, bone marrow infiltration or performance status did not differ in a study comparing 99 patients diagnosed prior to 1996 with 55 patients diagnosed from 1996 to 1999.[20] Systemic AIDS-related lymphomas show a number of differences from NHL in non-HIV-infected patients, including B symptoms and advanced stage disease, extra-nodal involvement,

Table 3. Factors associated with 2-year survival of human immunodeficiency virus-associated non-Hodgkin's lymphoma

	Survived (n=9)	Died (n=29)	p
Age (yr)	34.6 (33.5–39.8)	37.6 (33.8–38.3)	0.13
CD4 > 200 cells/μL	4 (44.4)	23 (79.3)	0.09
HIV PVL (log_{10}/mL)	4.37±1.60	4.59±1.47	0.58
Concurrent opportunistic infection	3 (33.3)	18 (62.1)	0.25
Concurrent malignancy	0 (0)	5 (17.2)	0.31
Receipt of C/T and/or R/T	9 (100)	14 (48.3)	<0.05
HAART initiated	9 (100)	19 (65.6)	0.08
HAART concomitantly with C/T or R/T	4 (44.4)	8 (27.6)	0.42
Deferred	5 (55.5)	2 (6.9)	
Prior AIDS status	5 (55.6)	24 (82.8)	0.17
Stage III/IV disease	5 (55.6)	25 (86.2)	0.07
International prognostic index	1.67±0.87	2.85±0.77	<0.05
lactate dehydrogenase (U/L)	467 (445–833)	1,281 (626–4,727)	0.06

[a]Data presented as n (%), median (interquartile range) or mean±standard deviation. CD4=cluster of differentiation 4; HIV=human immunodeficiency virus; PVL=plasma HIV RNA load; C/T=chemotherapy; R/T=radiotherapy; HAART=highly active antiretroviral therapy; AIDS=acute immunodeficiency diseases.

plasmacellular differentiation, and association with Epstein-Barr virus.[21] Extra-nodal involvement may be found at unusual sites, including the lung, oral cavity, visceral organs and CNS.[1] In this study, a high proportion of extra-nodal involvement was noted (84.6%) and the most common site was the CNS (47.4%), followed by bone marrow (26.3%), mucocutaneous sites, including skin and gingival (23.7%), and visceral organs (21.1%).

The survival of patients with HIV-associated NHL was poor in the pre-HAART era, but improved with introduction of HAART and the institution of chemotherapy at higher doses using improved treatment modalities. Biggar et al found that the 2-year survival rate of patients with NHL in New York city significantly improved from 1980 to 2000, increasing from 15% to 41% ($p < 0.0001$).[22] Another prospective observational study showed that 2-year survival rates improved from 29.0% in the pre-HAART era to 41.0% in the HAART era ($p = 0.12$; the lack of significance was probably due to inadequate sample size).[20] In this study, we did not see an improvement in 2-year survival rates in the HAART era. The most likely explanation for this is immunosuppression and a delay in NHL diagnosis. Nearly 40% of the patients died before chemotherapy or radiotherapy could be instituted. The median CD4 count in our HAART era patients (82 cells/μL; range, 2–453 cells/μL) was as low as that in the pre-HAART era patients (97 cells/μL; range, 3–477 cells/μL).

HAART, in combination with chemotherapy, is also important in the modern era for improved survival of patients with HIV-associated lymphomas.[23] However, our study did not show improved outcomes for patients receiving HAART in combined with chemotherapy or radiotherapy, but this may be attributable to the small sample size of this study. HAART therapy for more than 6 months was associated with a better outcome, suggesting that HAART given for a longer period of time restores immunity and prevents the relapse of lymphomas.[24]

There are several studies that predict the outcomes of HIV-associated NHL. Lim et al reported that IPI, which is a well established prognostic index for immunocompetent patients with intermediate-grade lymphoma, is also a good predictor of outcome in HIV-associated lymphomas.[25] Another study by Bower et al found that low, or low-intermediate IPI scores and CD4 cell counts of > 100 cells/μL were also good predictive factors.[26] Our study only supports IPI as a good predictive factor (the CD4 cell count was not statistically significant). This may also be due to the small sample size used in this study.

In conclusion, our findings suggest that the incidence of HIV-associated NHL significantly declined during the HAART era, although it still occurred in patients with advanced HIV infection. Despite the introduction of HAART, the short-term survival rate of patients with NHL remains poor, although the IPI is a good predictor for survival.

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