

Report of Aids-related Lymphoma in South Korea

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Received September 16, 2007; accepted November 24, 2007; published online February 8, 2008

Background: The prevalence of AIDS-related lymphoma (ARL) is increasing in South Korea. The aim of this study is to identify the clinical features of ARL in South Korea.

Methods: From 1998 through 2006, we retrospectively analysed a total of 23 cases of ARL from seven institutions.

Results: The patients consisted of 20 males and 3 females at a median age of 40 (range, 20–72) on diagnosis of AIDS. ARL developed at their median age of 41 (range, 24–72). The histological diagnosis was aggressive B cell lymphoma in the majority, but rare T cell and NK/T cell lymphoma were also included. Ten of 23 (43.5%) was receiving highly active anti-retroviral therapy (HAART) before the diagnosis of ARL. Fifteen of twenty-three patients were given combination chemotherapy with/without radiation, four were given radiation alone, and four did not receive any treatment against medical advice. Of 20 patients followed-up, nine were alive in remission, two alive in disease, one died of treatment related complication, four died of progressive lymphoma, four died of AIDS related causes. The response to treatment included CR in eight (44.4%), PR in four (22.2%) and PD in three (16.7%). The response to HAART was evaluable in 13 patients based on CD4+ cell count and HIV viral load, among which nine (69.2%) responded. Estimated median survival time was 43.9 months.

Conclusions: Although the population of patients is small, this is the first clinical data analyses of Korean ARL patients. As a substantial portion of the patients remains alive disease free, the impact of HAART on the clinical course of ARL needs further follow-up and evaluation.

Key words: lymphoma – AIDS-related – anti-retroviral therapy – highly active – chemotherapy – combination – radiotherapy

INTRODUCTION

Since 1985 when non-Hodgkin lymphoma (NHL) was included in the list of an acquired immunodeficiency syndrome (AIDS)-defining illness, the human immunodeficiency virus (HIV) epidemic has changed much. With the remarkable decrease in the incidence of opportunistic infections owing to the advent of highly active anti-retroviral

therapy (HAART), AIDS-related lymphoma (ARL) has emerged as the second most common cancer associated with HIV after Kaposi sarcoma (1). Recent large cohort studies showed that standardized incidence ratios for ARL were between 20 and 25 (2,3), findings indicative of a consistent increase in HAART era. Although HAART has resulted in a decline in the incidence of HIV-associated cancers as well, systemic NHL has remained a more common initial manifestation of the AIDS than ever (4). The World Health Organization has classified these AIDS-defining lymphomas into three categories: lymphomas also occurring in

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immunocompetent people, lymphomas more specifically related to HIV and lymphomas also occurring in other forms of immunodeficiency (5). Before the introduction of HAART, the prognosis of ARL was very poor, because the course of disease was more influenced by compromised immune status rather than by lymphoma *per se*. HAART has now proven as important component of therapy for ARL (6). The beneficial impact of HAART resides not only on the incidence of ARL but also on the therapeutic outcomes in ARL. This is partly due to the decrease in the incidence of opportunistic infections and also overall HIV-related mortality (7). The therapeutic strategy continues to improve in parallel with advance in insights into the pathophysiology as well as treatment modality.

As of December 2006, a total of 4580 cumulative AIDS patients were reported in South Korea to the Korean Center for Disease Control with continuous increase in annual incidence (8). The prevalence of ARL in South Korea must have increased as well in parallel with AIDS. We attempted to perform a retrospective analysis for an overview of ARL in South Korea on the behalf of Korean Society of Hematology Lymphoma Working Party (KSHLWP).

PATIENTS AND METHODS

PATIENTS

From August 1998 through July 2006, a total of 23 cases of ARL were treated at eight institutions participating in KSHLWP. A retrospective review of medical record of these patients using standardized case report form (CRF) was performed. CRF required all patients to be HIV-seropositive by enzyme-linked immunosorbent assay as well as confirmed by Western blot, and their lymphoma histologically or cytologically proven. Clinical data were analysed based on the clinical records and CRF including age, gender, Ann Arbor stage, B symptoms, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale, serum lactate dehydrogenase (LDH) level, cerebrospinal fluid analysis, prior diagnosis of AIDS, prior HAART, regimen of HAART, response to HAART measured by CD4+ cell count and HIV viral load, treatment of AIDS and ARL, response to initial treatment and histopathological subtype. The assessment of response was based on the International Workshop Response Criteria (9).

STATISTICAL ANALYSES

Overall survival (OS) was defined as the duration between the dates of diagnosis and death from any cause. Progression-free survival (PFS) was defined as the duration from the date of diagnosis to the date of disease progression, relapse or death from any cause. All survival curves were evaluated by the Kaplan–Meier method. A log-rank test was used in a univariate analysis to identify factors affecting survival. A *P*-value of 0.05 or less was considered to be

indicative of a statistical significance. All statistical analyses were performed using SPSS version 12.0.

RESULTS

PATIENT CHARACTERISTICS

The demographic and clinical characteristics of the 23 patients are summarized in Table 1. There were 20 male patients and three female patients with a median age of 41 years (range: 24–72) at the diagnosis of ARL and a median age of 40 years (range: 20–72) at the diagnosis of AIDS. A median interval between the diagnosis of AIDS and that of ARL was 7.6 months (range: 0–72.0). Eleven patients were given HAART before the diagnosis of ARL. Another eight patients were given HAART within 1 month from the diagnosis of ARL. And all the patients were eventually given HAART regardless of the time when the diagnosis of ARL was made. Eight patients presented with ARL as the primary AIDS-defining illness. None of the patients had a history of KS. The median CD4+ cell count was $46 \times 10^6/l$ (range, 3–368) and the median HIV viral load was 84 000 copies/ml (range, 1422–2 800 000). Nine patients (39.1%) had B symptom, 13 patients (56.5%) showed elevated serum LDH values. CSF study was done in eight patients, one of whom revealed evidence of lymphomatous meningitis. Eight

Table 1. Patient demographic and clinical characteristics

	Median (range)
Gender M/F	20/3
Age at AIDS diagnosis	40 (20–72)
Age at ARL diagnosis	41 (24–72)
Stage	
I	8 (34.8%)
II	4 (17.4%)
III	3 (13.0%)
IV	7 (30.4%)
unknown	1 (4.3%)
B symptoms	9 (39.1%)
ECOG Performance status	
0–1	11 (55%)
2–4	8 (40%)
Unknown	1 (5%)
Serum LDH level > normal	13 (56.5%)
CD4 count at diagnosis ($\times 10^6/l$)	46 (3–368)
HIV viral load at diagnosis (copy/ml)	84 000 (1422–2 800 000)

AIDS: acquired immunodeficiency syndrome
 ARL: AIDS-related lymphoma
 ECOG: Eastern Cooperative Oncology Group
 LDH: lactate dehydrogenase
 HIV: human immunodeficiency virus

Table 2. Pathologic diagnosis

Pathologic diagnosis	Number of patients
Diffuse large B cell lymphoma	14 (Primary CNS lymphoma, 4)
Burkitt lymphoma	2
Peripheral T cell lymphoma	2
Primary effusion lymphoma	1
Plasmablastic lymphoma of the oral cavity	1
NK/T cell lymphoma	1
Hodgkin lymphoma	1
B cell lymphoma, unclassified	1
Total	23

CNS: central nervous system

patients presented in stage I disease, four patients in stage II, three patients in stage III and three patients in stage IV (Table 1).

HISTOPATHOLOGICAL SUBTYPES

The results of the histopathological diagnoses of all the patients are summarized in Table 2. DLBCL including PCNSL was the most common histopathological ARL subtype (14 of 23 patients; 61%). Lymphomas associated more specifically with HIV were diagnosed in two patients (primary effusion lymphoma and plasmablastic lymphoma). Our series included diagnosis of uncommon T-cell lymphomas or Hodgkin lymphoma. A case of just 'B-cell lymphoma, unclassified' diagnosed on the biopsy from perianal skin lesion showed immunohistochemical staining positive for kappa light chain and negative for lambda light chain, CD20, CD45, CD3, CD30 and CD56. In this case, a possibility of plasmacytoma and plasmablastic lymphoma should be considered.

INITIAL TREATMENT

Among the 23 patients, four patients were not given any treatment because of poor general condition or patients' refusal. Standard dose CHOP chemotherapy (cyclophosphamide [CPA], doxorubicin [DOX], vincristine [VCR] and prednisolone [PRED]) was given to five patients. Chemotherapy using mBACOD (CPA, VCR, DOX, bleomycin [BLEO] and methotrexate [MTX]) was given to four patients and CEOP-B (CPA, epirubicin, VCR, PRED and BLEO) to 4. Two case of Burkitt's lymphoma were treated with CODOX-M/IVAC (CPA, VCR, DOX and MTX/ifosphamide, etoposide [ETO]) and EPOCH (ETO, DOX, VCR, CPA, PRED). Rituximab was not given to any patients. Seven of the 19 treated patients received radiotherapy (RT) at a median dose of 45 Gy (range: 30–60.4). Three patients who

Table 3. Treatment regimens

Regimen	Number of patients
CHOP	5
No treatment	4
RT only	4
CEOP-B	3
mBACOD	3
CODOX-M/IVAC	1
CVP	1
EPOCH	1
VAD	1
Total	23

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone
 mBACOD: methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine
 RT: radiotherapy
 CEOP-B: cyclophosphamide, epirubicin, vincristine, prednisolone and bleomycin
 CODOX-M/IVAC: cyclophosphamide, vincristine, doxorubicin and methotrexate/ifosphamide, etoposide
 EPOCH: etoposide, doxorubicin, vincristine, cyclophosphamide, prednisolone

had stage I or II disease received radiation therapy alone. Treatments for the patients are summarized in Table 3.

RESPONSE TO TREATMENT, SURVIVAL RATES

A total of 18 patients were available for the evaluation of their response to initial treatment. Five patients were excluded from the assessment for the reasons as follows: four patients with no treatment at all, and one patient lost to follow-up before response evaluation. The median follow-up duration was 9.2 months (range: 0.5–62.4). The overall response rate (ORR) for all evaluable patients was 66.7% as eight patients (44.4%) achieved CR and four patients (22.2%) achieved PR. Three patients (16.7%) whose diagnoses were DLBCL and PCNSL showed PD despite treatment.

Ten patients (43.5%) were alive at the time of the last follow-up. Nine of them showed no progression of disease including six patients in CR and three in PR after initial treatment. One patient who developed lymphomatous meningitis despite initial chemotherapy was alive receiving intrathecal (IT) chemotherapy at the time of last follow-up. One patient who showed CR after initial chemotherapy died of AIDS progression. One patient who showed PD on chemotherapy was lost to follow-up. The estimated OS of all 23 patients from the beginning of treatment was 43.9 months and estimated 3-year OS rate was 56.1%. (Fig. 1)

Response assessment of HAART by the titration of HIV viral copy number and/or the CD4+ cell count was available in 15 patients. Twelve patients (80.0%) showed sustained response, while three patients (20.0%) did not respond.

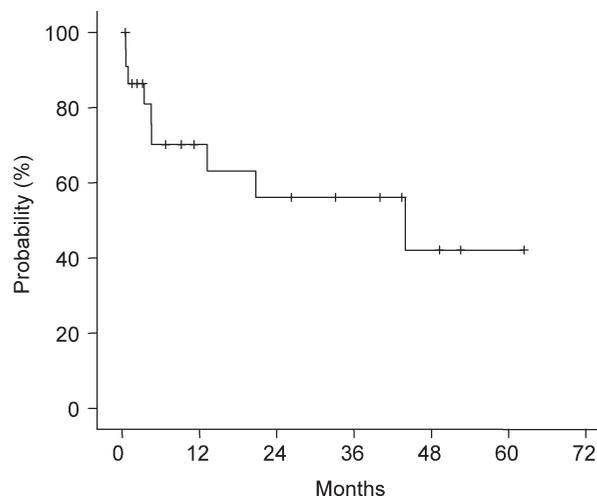


Figure 1. Overall survival of the patients.

There was a difference statistically not meaningful in the median survival duration (MSD) between two groups (not reached versus 20.7 months, $P = 0.34$).

PROPHYLACTIC MEASURES

Trimethoprim–sulfamethoxazole was given to 10 (55.5%) of 18 evaluable patients for *Pneumocystis jirovecii* prophylaxis. And IT chemoprophylaxis was given to only 2 (11.8%) out of 17 evaluable patients.

DISCUSSION

This is the first case series of ARL in South Korea. The incidence of ARL is so rare in AIDS-pauci area like South Korea that many important issues remain uninvestigated. There have been few reports on Korean ARL patients. The first report focused on spectrum of opportunistic infections

and malignancies in AIDS patients, and one with Primary CNS lymphoma (PCNSL) and one with tongue lymphoma were included (10). And the second one concerned about neurologic complications of HIV infection and two presumptively diagnosed as having PCNSL were included (11). A retrospective report showed that there were 13 NHL and 3 HD patients out of a total of 850 AIDS patients over 20 year period (12). But these data were from a single institution and lack of detailed information, such as histologic subtypes and treatments. Also we found few anecdotal reports published on Korean journals, one of them was included in this analysis in part (13), and clinical characteristics of the other patients are summarized in Table 4 (14–18). The spectrum of clinical presentation of ARL varies from localized disease confined in CNS or pleura to disseminated systemic disease. Our series showed a broad spectrum of clinical manifestations. The major histologic type was diffuse large cell lymphoma of B-cell phenotype; low grade histology was rare. It is of note that our series contain rare T-cell or NK/T cell lymphomas. Registry data from 11 American regions showed a rate of T-cell lymphoma of 1.4% from a total of 6788 cases of ARL (19). The majority included Mycosis fungoides and peripheral T-cell lymphoma.

Prognostic factors of ARL patients were amended after the introduction of HAART. Before the HAART era, the most important predictor of survival was the immune status, represented by the total number of CD4-positive lymphocytes (20). The uniformly poor prognosis of the ARL was related to the limitation in employing standard chemotherapy. The dose intensity of chemotherapy used in immune competent patients frequently aggravates existing profound immune compromise of ARL patients inviting severe infection (1). That explains why the aim of the chemotherapy in these patients was often palliative rather than curative. Once HAART was introduced, the immune function of the patients dramatically improved so as to alter the prognostic factors. Analysis of 111 patients treated with HAART indicated on

Table 4. Clinical characteristics of cases with ARL reported in South Korea

Author	Age/sex	Histologic subtype	Stage	Location	Prior AIDS diagnosis	Treatment	CD4+ cell count	HAART	Year	Reference
Song	33/M	Immunoblastic B cell lymphoma	IVAE	Bone	Yes	Radiation followed by mBACOD	53	Yes	1998	14
Han	52/M	Immunoblastic B cell lymphoma	N/A	Tongue	Yes	None	30	No	1999	15
Oh	63/F	Diffuse large B cell lymphoma	IAE	Stomach	Yes	Gastrectomy followed by COPP	125	N/A	2002	16
Choi	58/M	Burkitt lymphoma	IVA	Small bowel	Yes	CHOP	177	Yes	2004	17
Kim	59/M	Diffuse large B cell lymphoma	IVA	Systemic	Yes	CDE	41	Yes	2005	18

N/A, not available
 COPP: cyclophosphamide, vincristine, procarbazine, prednisone
 CDE: cyclophosphamide, doxorubicin, etoposide.
 HAART: highly active anti-retroviral therapy

regression modeling that only two independent predictors are valid, i.e. International Prognostic Index (IPI) risk group and CD4 cell count (21). Another study of ARL patients suggested prognostic value of HIV score based on performance status, history of prior AIDS, CD4+ cell counts (below 100/mm³, or above), IPI score and HAART with no relevance of CHOP-based chemotherapy dose intensity to the treatment outcome (22). Our series suggested that HAART response might be predictive of survival.

The treatment of HIV-related lymphomas is evolving in the era of HAART. Standard dose chemotherapy was thought inadequate for immune compromised ARL patients. However, the advent of HAART made it feasible not only to use standard dose but also dose intensification (4,23). The AIDS Malignancy Consortium (AMC) 005 trial, which compared combination chemotherapy (CHOP or reduced CHOP) and chemotherapy plus HAART showed that response rates and survival were improved in HAART group while adverse events were not different between the two groups (24). Surprisingly, CD4+ lymphocyte increased despite the chemotherapy and HIV viral load decreased during the HAART resulting in the decreased rate of opportunistic infections. Other approaches included infusional regimen such as EPOCH (25). In their trial, antiretroviral agents were stopped during chemotherapy, and resumed immediately at the completion of chemotherapy. Complete remission (CR) was achieved in 74% of patients with disease-free and overall survival of 92 and 60%, respectively, at a median follow-up of 53 months, the best results ever reported. They also found that the increase of CD4+ cell count over 100/mm³ was independent prognostic factor. The role of rituximab in patients with HIV infection is somewhat controversial. There were two randomized trials looking at the effect of rituximab in combination with chemotherapy. (26,27). In patients with higher CD4+ cell counts, the benefit of rituximab may outweigh its risk, although this has yet to be confirmed in prospective, randomized trials specifically performed in this population (28). In our study, none of the patients was given rituximab or infusional chemotherapy, because the majority of our patients were treated before the report of the landmark studies.

The incidence of central nervous system (CNS) involvement at presentation in patients with systemic ARL has ranged from 10 to 20% and that at relapse has ranged from 3 to 13% (29). Nowadays many experts are recommending prophylactic IT chemotherapy for ARL patients (1,27,30). They also emphasize supportive care measures vital in this patient population. These include use of hematopoietic stimulants such as G-CSF and erythropoietin for alleviation of chemotherapy induced marrow suppression as well as trimethoprim-sulfamethoxazole for *P. jirovecii* prophylaxis. In our series, many of the patients did not receive IT prophylaxis, but *P. jirovecii* prophylaxis.

In conclusion, we report here the clinical features of ARL patients in South Korea which are different from those reported in western countries in distribution of pathologic

subtype, although small population of the study limited statistical analysis. Given the increasing number of lymphoma as the presentation of the AIDS defining illness, a high index of suspicion for ARL is required by clinicians caring for patients with HIV infection as well as lymphoma, paying attention to their non-specific presentation. A nationwide survey of ARL must be conducted to gain further insight into the current status in Korean ARL patients.

Funding

This study was supported by Inha University Research Grant.

Conflict of interest statement

None declared.

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