Human Immunodeficiency Virus – Associated Lymphomas: A Neglected Domain

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Abstract

Background: Human immunodeficiency virus (HIV) associated lymphoma is an important public health concern; however, the epidemiological data available from India is sparse. Aims: The present study was carried out at a tertiary cancer care center in South India to analyze the scenario of HIV-associated lymphoma. Materials and Methods: This was a retrospective observational study conducted at our center, on consecutive patients diagnosed with HIV-associated lymphoma, from January 2008 to December 2012. Results: A total of 44 patients were diagnosed with HIV-associated lymphoma, of which 18 opted for treatment. There were 11 males and 7 females in the study population. Median interval from the diagnosis of HIV infection to diagnosis of lymphoma was 18 months. Median CD4 count at the time of lymphoma diagnosis was 218/mm³. Five patients had Hodgkin’s lymphoma, and the rest had non-Hodgkin’s lymphoma. Five out of 18 (28%) patients in the present study expired during treatment. Ten (55.5%) patients are alive and lymphoma free, with a median follow up of 18 months. Conclusions: More than half of our treated patients are lymphoma free with a median follow up of 18 months; hence treatment of patients with HIV-associated lymphoma should be encouraged.

Keywords: Acquired immunodeficiency syndrome, Adriamycin bleomycin vinblastine dacarbazine, CD4 count, Human immunodeficiency virus, Lymphoma, Rituximab cyclophosphamide doxorubicin vincristine and prednisolone

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Introduction

Human immunodeficiency virus (HIV) associated lymphoma was initially included in the United States Center for Disease Control and Prevention’s (CDC) case definition of Acquired immunodeficiency syndrome (AIDS) in 1985. HIV-infected patients are at increased risk for developing both Hodgkin’s lymphoma (HL) and non-Hodgkin’s lymphoma (NHL), as compared to the general population. The added risk of high-grade NHL among HIV patients was first reported in 1984 by Ziegler et al. HIV infected patients are more likely to present with extra nodal NHL and high-grade histologies. India has an immense burden of 2.4 million people infected with human immunodeficiency virus type 1 (HIV-1) making it the third largest country with HIV-1 infected population. In the pre-HAART (highly active anti-retroviral therapy) era, the median survival of patients with HIV-associated lymphoma with CD4 count less than 100 cells/mm³ was about 4 months, and those with CD4 > 100 cells/mm³ had a median survival of 11 to 18 months. Following the advent of HAART, survival has increased twofold. Using the current treatment regimens, treatment results of high-grade B-cell NHLs among HIV-infected patients, have caught up with the general population, especially in diffuse large B cell lymphoma (DLBCL) and Burkitt’s lymphoma (BL).
However, the treatment of patients with HIV-associated lymphoma presents the challenge of integrating therapy appropriate for the stage and histological subset of malignant lymphoma, with the limitations imposed by HIV infection, which till date, is incurable. Although HIV-associated lymphoma is an important public health concern, there is limited epidemiological data from India due to under reporting. The present study was carried out at a tertiary oncology care center in South India, to analyze the scenario of HIV-associated lymphoma, and also to assess what percentage of patients diagnosed with HIV-associated lymphoma opted for treatment.

**Materials and Methods**

This was a retrospective observational study carried out at a tertiary cancer care in South India. With the concurrence of the institutional ethics and review board (IERB), we included consecutive patients diagnosed with HIV-associated lymphoma from January 2008 to December 2012. Patients were either diagnosed cases of HIV infection receiving HAART who presented to our center for management of lymphoma, or were diagnosed with HIV during work up for lymphoma at our institute. The case records of individual patients were analyzed for demographic and clinical details regarding age and gender of patients, site of involvement (nodal-extra nodal), clinical staging, pathologic subtype of HL and NHL, CD 4 count at the time of lymphoma diagnosis, median duration from HIV diagnosis to lymphoma occurrence in patients with previously diagnosed HIV infection, treatment instituted, response to therapy, complications during treatment and treatment outcome. Patients were followed up using details mentioned in case records (last follow up). For patients who declined treatment and for those who were lost to follow up after diagnosis of HIV-associated lymphoma, follow up status was assessed with contact number/address registered in file records.

**Statistical analysis**

All variables were entered on Microsoft excel/Statistical Package for Social Sciences 15 (SPSS 15). Calculation of mean, median and range was done using Microsoft excel, and median survival was calculated based on the time from lymphoma diagnosis to death due to any cause. Disease free survival was based on the length of time that the patient survived without any signs or symptoms of lymphoma after completing the primary treatment.

**Results**

A total of 44 patients were diagnosed with HIV-associated lymphoma during the period from January 2008 to December 2012. Twenty six of these 44 patients were newly diagnosed cases of HIV infection, and diagnosed to have HIV infection during work up for lymphoma at our institute. None of these 26 patients, who initially presented for treatment of lymphoma, came back for treatment after they got acquainted with the diagnosis of HIV infection. Of the 26, 18 were males and 8 were females and their mean age was 38 years (range 29-51 years). We were able to get a follow up of 9 of these 26 patients. The median survival of these patients was 7 months. We were unable to analyze histological subtypes and median CD4 count in these patients, as they did not undergo complete work up after being diagnosed with HIV infection.

There were 18 patients who were previously diagnosed cases of HIV infection on HAART, and were diagnosed to have lymphoma at our institute. Interestingly, all of these 18 patients opted for lymphoma treatment in contrast to patients diagnosed with HIV and lymphoma concurrently. There were 11 male and 7 female patients. Median age of these 18 patients was 39.5 years (range 27-62 years). Median time interval from diagnosis of HIV infection to diagnosis of lymphoma was 18 months (range 8-26 months). CD4 count at the time lymphoma diagnosis was in the range of 38-316/mm\(^3\), with a mean value of 218/mm\(^3\). Five patients had HL and the remaining patients had NHL. Twelve out of 18 (66.7%) patients had stage III/IV disease. All NHL patients had high grade NHL (Table 1 shows histological subtypes of HIV-associated lymphoma). Eight out of the 13 (61.5%) patients with NHL had extra nodal involvement (Table 2 shows clinical pattern of HIV-associated lymphoma in present study). Seven patients had B symptoms. Patients with HL received ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine) chemotherapy while NHL patients received either CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) or R-CHOP (Rituximab-CHOP). Patients with primary central nervous system lymphoma (PCNSL) were treated with De Angeli’s protocol. Two patients had plasmablastic lymphoma of oral cavity, and were treated with CHOP regimen followed by radiotherapy. All patients continued HAART along with chemotherapy and were

| Table 1: Histological subtypes of human immunodeficiency virus-associated lymphomas in present study |
|---------------------------------------------------------------|
| **Histological subtype** | **Number of patients (n=18)** |
| Hodgkin’s lymphoma | 5 (27.8%) |
| Mixed cellularity | 5 |
| Non-Hodgkin’s lymphoma | 13 (72.2%) |
| Diffuse large B cell lymphoma | 9 (50%) |
| Plasmablastic lymphoma | 2 (11.1%) |
| Primary central nervous system lymphoma | 2 (11.1%) |
given *pneumocystis jiroveci* pneumonia prophylaxis (Table 3 shows treatment given and treatment outcome in present study).

2 patients with HL had Ann Arbor stage II while 3 had stage III lymphoma. Out of 13 NHL patients 2 had Ann Arbor stage I, 2 had stage II, 4 had stage III and 5 had stage IV lymphoma. Extra nodal involvement included tongue in one patient, alveolar part of mandibular ramus in one patient, stomach in one patient, soft tissue in two patients and CNS in four patients.

**Discussion**

Prevalence of HIV in India reflects a high disease burden. The Center for Disease Control definition of AIDS - defining lymphoma in 1993 as Burkitt’s lymphoma, immunoblastic lymphoma and primary brain lymphoma, is based on older terminology. AIDS related lymphomas are a histological heterogeneous group of aggressive mature B-cell neoplasms, and are classified using current World Health Organization criteria.\(^9\) They are classified as lymphomas also occurring in immunocompetent patients [which includes Burkitt’s lymphoma, Diffuse large B-cell lymphoma, Extra nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue lymphoma (rare), Peripheral T-cell lymphoma (rare), Classic Hodkgin’s lymphoma, Lymphomas occurring more specifically in patients who are HIV positive [which includes Primary effusion lymphoma, Plasmablastic lymphoma of the oral cavity], and Lymphomas occurring in other immunodeficiency states such as Polymorphic B-cell lymphoma.

The risk of developing lymphoma in HIV-infected patients in the pre-HAART era was more than 250-fold greater than the general population. Since the advent of HAART, the incidence of NHL has decreased by approximately 50%.\(^10\) Nonetheless, NHL is still a very common malignancy in HIV-infected individuals. Venkatesh et al.\(^11\) in their analysis of spectrum of malignancies among HIV-infected patients in South India had reported that the most common type of cancer in HIV-infected patients was NHL (38.1%), followed by HL (16.7%). In the present study of 44 cases with HIV-associated lymphomas, 26 patients were detected to be HIV positive at the time of work up for lymphoma at our institute. This highlights the fact that lymphoma can be the initial manifestation of HIV. Also there may be a possibility that these patients may not be aware of voluntary counseling and testing (VCT) centers, and so did not get themselves tested for HIV previously. VCT should be promoted for an effective control of HIV spread in areas with generalized HIV epidemic.\(^12\) More than 80% of lymphomas occurring in HIV-infected patients are high-grade mature B-cell lymphomas,\(^13\) including DLBCL, Burkitt’s lymphoma, plasmablastic lymphoma, PCNSL and primary effusion lymphoma. In contrast, these histologies constitute 22% to 26% of lymphomas in the general population.\(^14\) This was evident in the present study as well. 12 out of the total 18 (66.7%) patients in present study had high grade B-cell NHL. Similar observation was made by Sharma et al.\(^15\) in their analysis of HIV-associated NHL.

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The mean age of 18 patients in present study was 39.5 years (range 27-62 years), with 11 patients being male and 7 female. In the study of Venkatesh et al.,\(^11\) the median age at the time of cancer diagnosis in HIV-infected patients was 35 years (range 29.8-46.3 years). Over two-thirds (69%) of patients in their study were males. Sharma et al.\(^15\) in their analysis of 7 patients of HIV-associated NHL reported median age at the time of lymphoma diagnosis of 38.57 years (range 14-56 years). They also have reported male preponderance, with 5 out of the 7 patients in their study being males. Analysis of

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**Table 2: Clinical pattern of human immunodeficiency virus-associated lymphomas in present study**

| Pattern of involvement by lymphoma | Number of patients (n=18) |
|-----------------------------------|--------------------------|
| Hodgkin’s lymphoma                | 5                        |
| Nodal                             | 5                        |
| Extra nodal                       | 0                        |
| Non-Hodgkin’s lymphoma            | 13                       |
| Nodal                             | 5 (38.5%)                |
| Extra nodal                       | 8 (61.5%)                |

**Table 3: Treatment given and treatment outcome in present study**

| Treatment given | Number of patients | Treatment outcome |
|-----------------|--------------------|-------------------|
| ABVD            | 5                  | 1 died during treatment; 1 lost to follow up after being DF for 9 months, 3 alive and DF (median follow up 21 months) |
| CHOP            | 5                  | 2 died during treatment; 3 alive and disease free (median follow up 18 months) |
| RCHOP           | 6                  | 1 died during treatment; 1 lost to follow up after 6 cycles (was in CR); 1 lost to follow up after being DF for 15 months; 3 alive and DF (median follow up 18 months) |
| De Angeli’s protocol | 2            | 1 died during treatment; 1 alive and disease free (13 months follow up) |

ABVD: Adriamycin; bleomycin; vinblastine; dacarbazine; chori: cyclophosphamide; doxorubicin, vincristine; prednisolone; r-chori: rituximab; cyclophosphamide; doxorubicin; vincristine; prednisolone; DF: (Disease free i.e., free from lymphoma); CR: Complete remission (no evidence of lymphoma after therapy)
this Indian data reveals that HIV-associated lymphomas occur more commonly in fourth decade of life, and males are more commonly affected than females. In review of western literature, Diamond et al. [16] have reported median age of HIV-associated NHL as 39 years, with male to female ratio of 10:1. Chow et al. [17] have reported median age of HIV-associated NHL as 44 years, with male to female ratio of 49:1. This male preponderance in all these studies may be a reflection of higher incidence of HIV positivity in the male population.

CD4 count is regarded as one of the indices for monitoring the response of HIV/AIDS patients to HAART. [18] Risk of HIV-associated lymphoma is inversely related to the CD4 cell count, although the relationship varies among different lymphomas. [19,20] PCNSL often develops in patients with very low CD4 counts, while DLBCL and Burkitt’s lymphomas are generally present in patients with higher CD4 counts. In this study, CD4 count at the time lymphoma diagnosis was in the range of 38-316/mm$^3$, with a mean value of 218/mm$^3$. Sharma et al. [15] have reported mean CD4 count 243/mm$^3$ (range 18-454) in their analysis of 7 patients of NHL. In our study, median time interval from diagnosis of HIV infection to diagnosis of lymphoma was 18 months (range 8-26 months). Venkatesh et al. [11] have observed that the median duration of time from HIV infection to cancer diagnosis was 549 days.

Patients with HIV-associated HL generally present at a younger age, with advanced disease, frequent extra nodal involvement and “B” symptoms as compared to the general population. Immune status is often relatively good, with a median 275 CD4 cells/mm$^3$. [21] Mixed cellularity or lymphocyte-depleted histology is commonly seen, in comparison with nodular sclerosis histology seen in HIV-negative patients. [21,22] In general, complete response rates in HIV-associated HL are relatively high with systemic chemotherapy (50% to > 80%). The conventional ABVD therapy is used commonly. In this study, there were 5 cases of HL, all being mixed cellularity type with a median CD4 count 264 cells/mm$^3$ (range 234-389/mm$^3$). None of our patients had extra nodal disease, 2 patients had Ann Arbor stage II disease and 3 patients had stage III disease. All 5 patients were treated with ABVD chemotherapy. One patient died during treatment; one was lost to follow up after being disease free for 9 months, while three patients are alive and disease free with a median follow up of 21 months. Complete response rate with ABVD in present study was 80%.

HIV-associated NHL frequently presents with extra nodal involvement, including bone marrow (25% to 40%), gastrointestinal tract (26%), and CNS (12% to 57%) involvement. [13] In our study, we noted that 8 out of the 13 (61.5%) patients with NHL had extra nodal involvement. HIV-associated plasmablastic lymphoma (PBL) has a reported 7:1 male predominance, and median CD4 count at diagnosis of 178 cells/mm$^3$. [23] PBL is characterized by a high proliferative index and aggressive clinical course. Historically, the prognosis has been poor, with median survival less than 2 years. CHOP is not much beneficial. CODOX-M/IVAC, Dose Adjusted - etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) regimens are recommended for treatment of plasmablastic lymphoma. There were 2 patients with plasmablastic lymphoma of oral cavity in the present study (one 35 years female with PBL of alveolar part of ramus of mandible-CD4 count 249 and one 55 year male with PBL of oral tongue- CD4 count 264; both Ann Arbor IEA), who were treated with CHOP chemotherapy followed by radiotherapy. One succumbed to the illness during radiotherapy, while the other is alive and disease free with a follow up of 33 months.

AIDS-related Primary CNS lymphoma (PCNSL) almost always occurs in patients with a CD4 count of less than 50 cells/mm$^3$. CNS involvement in HIV patients apart from lymphoma can be due to meningitis, viral encephalitis, AIDS dementia complex, progressive multifocal leukoencephalopathy and toxoplasmosis. [24] Definitive diagnosis of PCNSL requires stereotactic biopsy. However, detection of Epstein-Barr Virus (EBV) Deoxyribonucleic acid (DNA) by polymerase chain reaction in the Cerebrospinal fluid (CSF) combined with positive brain $^{201}$TI single-photon emission computed tomography has been shown to reliably predict the presence of PCNSL. There were 2 patients of PCNSL in present study (CD4 count 38/mm$^3$ and 68/mm$^3$). Both these patients had presented initially to the division of neurosurgery with hemi paresis and underwent decompression of intracranial mass, and were then referred to our institute, as the histopathology report revealed malignant lymphoma. Both patients were treated with De Angeli’s protocol which includes high dose methotrexate, steroids and procarbazine, in addition to whole brain radiotherapy. One patient died during treatment due to febrile neutropenia and multiorgan failure, while the other is alive and disease free with 13 months follow up.

DLBCL is the most common HIV-associated NHL. [25] Kaplan et al. have reported complete remission (CR) rate of 47% with CHOP. [26] Ratner et al. [27] have reported that the CR rates were 30% and 48% among patients who received modified CHOP and full-dose CHOP combined with HAART, respectively. Liposomal doxorubicin in combination with cyclophosphamide, vincristine, and prednisone achieved CR in 75% patients,
and the median duration of CR was 15.6 months (range 1.7-43.5 months). Consensus exists that rituximab should also be used in CD20-expressing lymphomas in the setting of HIV. Ribera et al. reported that the complete remission rate in DLBCL was 69% with R-CHOP, and the estimated 3-year overall survival was 56%. We could not give Rituximab to all our patients due to financial constraints. R-CHOP was given to 6 patients. 1 died during treatment; 1 lost to follow up after 6 cycles (was in CR); 1 lost to follow up after being DF for 15 months; and, 3 are alive and disease free with a median follow up of 18 months.

In addition to chemotherapy, essential components of an optimal treatment strategy include HAART, prophylaxis against opportunistic infections, and early recognition and treatment of intercurrent infections. All our patients continued to use HAART along with chemotherapy and pneumocystis jiroveci pneumonia prophylaxis was given to all patients during treatment. There were several practical issues encountered while treating these patients. Treatment with HAART is complicated by pharmacokinetic drug interactions which often require dose modifications. Immunodeficiency and cytopenias, common in these patients at the time of initial presentation, are exacerbated by the administration of chemotherapy. Treatment of the malignancy therefore increases the risk of opportunistic infections, which in turn further compromises the delivery of adequate treatment that alters treatment outcome. 5 out of 18 (28%) patients in this study died during treatment due to complications of febrile neutropenia and multiorgan failure. In almost all patients, prolonged neutropenia following chemotherapy, caused a delay in scheduled chemotherapy protocol. Granulocyte colony stimulating factor (G-CSF) was used in 11 (61.1%) patients. Similar complications were seen in the study by of Sharma et al., as well requiring significant dose modifications.

Conclusions

HIV-associated lymphoma is an important public health concern, and we need to improve epidemiological surveillance in our country for understanding the prognosis and improving outcome in this subset of malignancy. Treatment of HIV-associated lymphoma is often complicated by prolonged neutropenia and infectious complications, and requires vigorous supervision after chemotherapy, frequent use of growth factors and antibiotics in contrast to treatment of lymphoma in immunocompetent patients. More than half of our treated patients are lymphoma free with a median follow up of 18 months; hence treatment encouragement is needed in all patients with HIV-associated lymphoma.

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How to cite this article: Sirsath NT, Channaviriappa LK, Nagendraappa LK, Dasappa L, Sathyanarayanan V, Setty GK. Human Immunodeficiency Virus - associated lymphomas: A neglected domain. North Am J Med Sci 2013;5:432-7.

Source of Support: Nil. Conflict of Interest: None declared.