HIV Associated Lymphomas

University of Texas Southwestern Medical Center

Conflict of Interest

This is to acknowledge that Harris V Naina MD does not have any financial interests or other relationship with commercial concerns related directly or indirectly to this program. Dr.Harris V Naina will not be discussing off label uses in his presentation.

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Area of Interest – Lympho proliferative disorders and HIV associated lymphomas

Purpose and Overview of HIV Associated Lymphomas

Purpose of this grand round is give a brief overview of human immunodeficiency (HIV) associated lymphomas, clinical presentation and commonly used treatment modalities. In this presentation I will be discussing on 5 most common lymphomas associated with HIV.

I will be discussing epidemiological data and pathogenesis of HIV associated lymphomas. I will discuss on 5 most common lymphoma diffuse large B cell lymphoma, Burkitt lymphoma, plasmablastic lymphoma, primary effusion lymphoma (PEL) and Primary central nervous system (CNS) lymphoma. Presentation will be small case based with imaging studies and histopathology review.

Objective

1. To highlight the association of HIV and lymphomas

2. Association of Epstein Barr Virus (EBV) and Human Herepes Virus (HHV8) and HIV associated lymphomas.

3. Current chemotherapeutic regimens used in HIV associated lymphomas and clinical outcome with different combination chemotherapy

Introduction

Persons with human immunodeficiency virus (HIV) infection are at risk for numerous medical complications, particularly AIDS, which can result in death. Early in the HIV epidemic, persons with AIDS had markedly increased risks of Kaposi sarcoma (KS) (50 000-fold risk compared with the general population), cervical cancer (8-fold), and 3 subtypes of non-Hodgkin lymphoma (NHL): diffuse large B-cell lymphoma (DLBCL) (98-fold), Burkitt lymphoma (BL) (57-fold), and central nervous system (CNS) lymphoma (5000-fold). These 5 malignancies are included in the 1993 US Centers for Disease Control and Prevention (CDC) AIDS definition. Diagnostic classification of lymphomas has evolved during recent years, and immunoblastic lymphoma as noted in the CDC definition is now considered a variant of DLBCL. As the survival of people living with HIV increases, malignancy has become a leading cause of death in this population.

Between 25% and 40% of people living with HIV will develop cancer, with $\sim$10% attributed to ARL; infection-related cancer is likely to become an increasingly important complication of long-term HIV infection.

Following table shows the most common HIV associated lymphomas.

Relationship of HIV-associated lymphomas with EBV and KSHV-associated lymphoproliferative disorders.

EBV-associated B-cell lymphoproliferative disorders
HIV-associated lymphomas
Immunodeficiency-associated BL-plasmacytoid
Primary central nervous system lymphoma
DLBCL, immunoblastic
KSHV-positive PEL and its solid variant
Plasmablastic lymphoma
Other histotypes (rare)[a]
KSHV-associated lymphoproliferative disorders
HIV-associated lymphomas
KSHV-positive PEL and its solid variant
Classic PEL – in the absence of tumor masses
Solid PEL[b] with serous effusions
Solid PEL[b] without serous effusions
MCD-associated plasmablastic lymphomas
Other
Germinotropic lymphoproliferative disorder
Lymphomas with controversial association with KSHV

Abbreviations: BL, Burkitt's lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; KSHV, Kaposi sarcoma herpesvirus; MCD, multicentric Castleman's disease PEL, primary effusion lymphoma.

[a] Other histotypes include: lymphomatoid granulomatosis, DLBCL associated with chronic inflammation, EBV-positive DLBCL of the elderly.

[b] Formally termed extracavitary KSHV positive solid lymphoma.

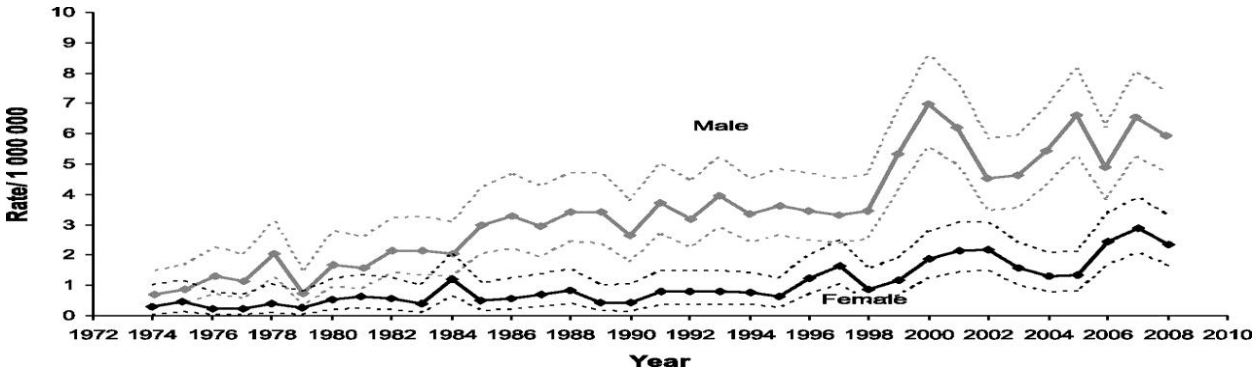
Epidemiology

Burkitt Lymphoma

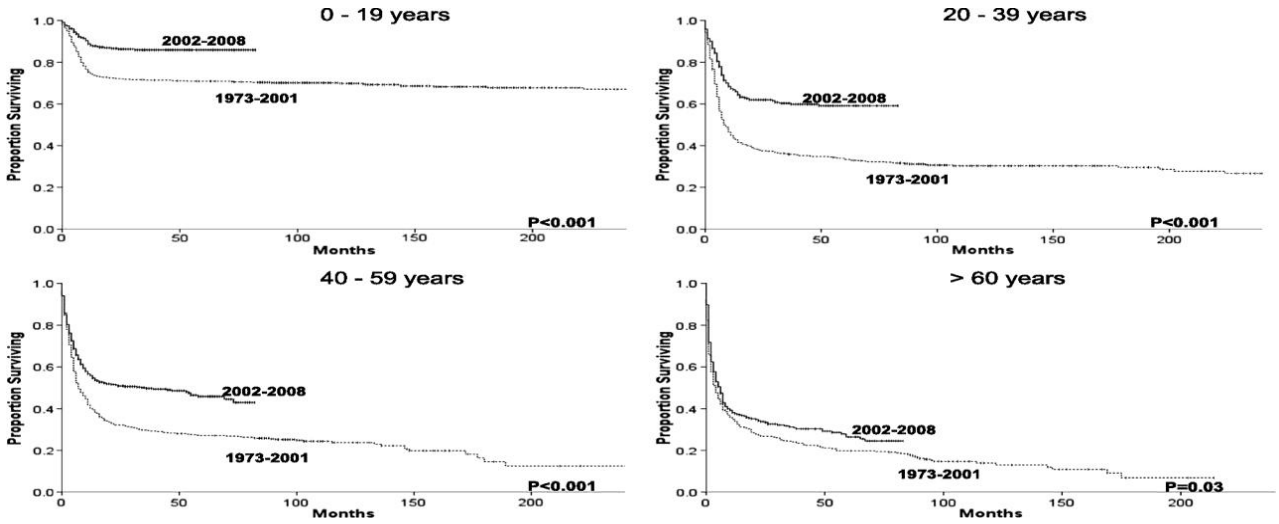
Since the mid-1980s, the epidemiology of Burkitt lymphoma (BL) in the United States has been vastly affected by the epidemics of HIV infection. Patients living with HIV are 57 times more likely to develop BL than HIV-negative individuals. In the United States, approximately 20% of the cases of BL are in individuals with HIV.

It is unknown to what extent the recent availability of adequate antiretroviral therapy (ART) has impacted the survival expectancy of patients diagnosed with BL in the United States. Using data from the Surveillance Epidemiology and End Results (SEER) program, Sheils et al. described overall survival for patients with BL in 2 distinct eras based on year of diagnosis, 1973-2001 and 2002-2008, reflecting the development of intense chemotherapy regimens, availability of rituximab, and adequate ART for HIV+ patients. The latter was expected to reflect the implementation of multi agent intense chemotherapy regimens, availability of rituximab, potential improvements in supportive care, and broad use of modern ART. Even though this is not primarily an incidence study, knowledge of the pattern of incidence of BL is helpful in interpreting the findings of the survival analysis. As displayed in Figure , there was a marked increase in BL

incidence starting in the late 1980s, and predominantly affecting men for whom, in 2008, it reached a rate of 5.95 per 1 000 000 (95% CI = 4.74-7.39). This increase is believed to be linked, at least in part, to the AIDS epidemic, a disease that disproportionately affects men. In fact, the incidence of BL among women appears only to increase substantially in the mid-1990s and, in 2008, reached a rate of 2.36 per 1 000 000 (95% CI = 1.64-3.28).



Overall, there was a significant improvement in relative survival at 5 years after diagnosis of BL from 43% (95% CI = 40-45) in the 1973-2001 era to 56% (95% CI = 53-58) in the 2002-2008 era. Absolute 5-year survival also improved from 41% (95% CI = 39-44) in the 1973-2001 era to 54% (95% CI = 51-56) in the 2002-2008 era.



Improvements in survival across eras occurred in all races *but outcomes for black patients remain significantly inferior to outcomes for whites, even within the most recent era*

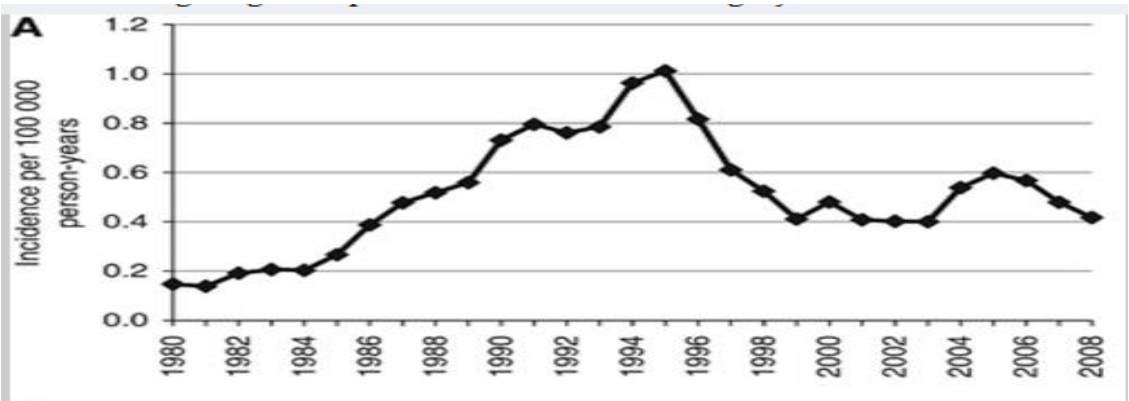
Another SEER data showed improved survival for patients with BL diagnosed in the United States since the development of intense chemotherapy regimens, availability of

rituximab, and implementation of effective ART. However, *this study points to the need of better access to complex care particularly for adult and black patients and the need for differential treatment strategies appropriate for older patients with BL.*

Primary CNS lymphoma

Primary central nervous system lymphoma (PCNSL) is a rare disease that accounts for approximately 3–4% of newly diagnosed central nervous system (CNS) tumors. The age-adjusted incidence rate has previously been reported at four cases per million persons per year, or ~1200 cases per year in the United States. A prominent risk factor for the development of PCNSL is immunodeficiency, which includes congenital disorders, iatrogenic immunosuppression, and most notably, HIV. PCNSL is one of the four AIDS-defining malignancies and HIV infection carries a 3600-fold increased risk of developing the disease compared with the general population. The outcome of PCNSL patients is dismal compared with patients with systemic DLBCL, where greater than 50% are long-term survivors. It is unclear if this is attributable to an intrinsic aggressive biological behavior, the relatively immune-privileged CNS location or to some other yet undetermined cause. Outcomes are also different in HIV/AIDS-related PCNSL having a median survival of 2 months *vs* a year for non-HIV-related PCNSL. HIV/AIDS disproportionately affects blacks, by greater than an order of magnitude than other race groups, as well as young adults.

Analysis by a broad age group of 0–49 and 50+ years demonstrate differences in incidence by race. The 0–49-year group of black males had greater than twice the incidence of white males, whereas the 50+-year group of white males had greater than twice the incidence of black males. Although the number of cases was less, the same pattern was present for black females. This indicates that blacks have a lower incidence of the advanced age (presumed non-HIV)-related PCNSL, which is consistent with the lower incidence of systemic lymphomas in blacks.



Incidence rate trends over time for (A) CNS lymphomas; SEER onine registries research data, 1980–2008.

Primary Effusion Lymphoma (PEL)

PEL is an unusual lymphoproliferative disorder, accounting for 2% or less of HIV-associated lymphomas, and is even more rarely encountered in the HIV-seronegative patient. PEL is divided into classic and solid variants. Primary effusion lymphoma is a large cell non-Hodgkin lymphoma localized predominantly in body cavities and occasionally in extracavitary regions. It presents with characteristic lymphomatous effusions in the absence of solid tumor masses, and pleural, peritoneal, and pericardial spaces are most often involved. It is characteristically associated with human herpesvirus 8 (HHV8) infection; coinfection with Epstein-Barr virus (EBV) is commonly found. Kaposi's sarcoma first described by Moritz Kaposi in 1872 as "idiopathic multiple pigmented sarcomas of the skin. Previously a rare disease, it is now a global health care and clinical problem because of its association with the HIV pandemic and other immunosuppressed states. In 1994 a previously unrecognized γ-herpesvirus was discovered by Chang and Moore using representational difference analysis to identify DNA fragments of this virus from Kaposi sarcoma (KS) tissue samples. Named Kaposi sarcoma–associated herpesvirus (KSHV), and also known as human herpesvirus-8 (HHV-8), KSHV was subsequently also identified in primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD) samples.More than a coincidental finding, KSHV infection is a requisite for the development of KS and PEL, and is the pathogenic stimulant for many cases of MCD, including all HIV-associated MCD. In addition to these three aforementioned ‘hallmark’ diseases, other conditions, such as hemophagocytic lymphohistiocytosis have been associated with KSHV. Although infection with KSHV is necessary for the development of KSHV-associated disease, it is not sufficient. Both HIV coinfection and immunosuppression significantly increase the risk of KSHV-associated disease.

Plasmablastic lymphoma

PBL is classified as a distinct entity by the World Health Organization and typically occurs in the oral cavity in the clinical setting of HIV infection, accounting for 2.6% of NHLs in this population. This lymphoma was first described in the jaws and oral cavity of HIV-infected persons. These lymphomas have subsequently been reported in many other extranodal sites of HIV-positive individuals. This rare entity typically involves the jaw and oral cavity of HIV patients even if it has been documented in other sites than the oral cavity such as the anorectum, nasal and paranasal regions, skin, testes, bones, and lymph nodes. PBLs of the oral cavity type are composed of large neoplastic cells with a very high proliferation rate displaying a marked degree of plasma cell differentiation. Nodal involvement has been reported, but is uncommon. These lymphomas are rapidly growing; EBV appears to be highly associated (60–75% of cases) with plasmablastic lymphoma. The presence of KSHV in PBLs is unlikely; most reports have indeed shown that PBLs do not contain KSHV. The mitotic rate is very high, and there are frequent apoptotic cells and single-cell necrosis. The destructive tumors that exhibit a proliferation index ranging from >60% to 95%. PBL of the oral cavity type consists of a monomorphic population of plasmablasts/immunoblasts with no or minimal plasmacytic differentiation. Cells with features of maturing plasma cells can be seen and there is usually a spectrum of differentiation than can be appreciated morphologically.

Plasmablasts are typically negative for CD45, CD20, and/or PAX5, may be immunoreactive for the B-cell marker CD79a, and demonstrate strong immunoreactivity for plasma cell markers (VS38c, CD38, IRF4/MUM-1 or CD138). HIV-associated PBL tends to affect young men with CD41 counts less than 200 cells/mm3. The consistent presence of plasma cell markers and frequent absence of B-cell markers are key pathologic features of this entity. The association of PBL with EBV is higher than that with HHV8. Despite a good initial response to therapy, the rate of recurrence is high, and the prognosis remains poorer than that of other DLBCL subtypes.

Diffuse large cell B-cell lymphoma

HIV-1 increases the risk for systemic diffuse large cell B-cell lymphoma **(**DLBCL) the most common form of ARL, by 60- to 200-fold. The pathogenesis of ARL is linked to the immunosuppression caused by HIV BV-associated DLBCLs have therefore been considered as EBV-driven lymphoproliferations occurring in the context of a defective T-cell immunity against EBV.

Liapis et al. investigated the tumor, microenvironment, and viral components in 41 AIDS-related diffuse large B-cell lymphomas (AR-DLBCLs) in the pre- and post-HAART era. Among HIV-infected patients, 22% had centroblastic, 48.8% immunoblastic, 9.7%

plasmablastic lymphoma, and in the remaining 19.5% the histology was unclassified. Before HAART, immunoblastic DLBCL was seen in all cases whereas after HAART this decreased to 27.6%. Immunoblastic/plasmablastic morphology was associated with an adverse outcome ($P < .001$). Among patients without HIV, centroblastic DLBCL accounted for 69.7% and immunoblastic for 11.7%, whereas unclassified cytology was noted in 18.6%. The immunophenotypic classification into germinal center (GC) and non-GC types was based on CD10, bcl-6, MUM1, with inclusion of CD138. Regarding antiapoptotic proteins, bcl-2 positivity and p53 overexpression were found in 44% and 47.2% of AR-DLBCL, respectively. Hyperproliferation was significantly more likely to occur in HIV-infected patients ($P < .001$). Rearrangements involving c-Myc were identified in 23.5% and 5.6% of HIV-infected and sporadic samples, respectively. c-Myc rearrangement was associated with hyperproliferation ($P = .024$) but no correlation was detected with lymphoma immunophenotype, morphology, p53, and aaIPI. In fact, AR-DLBCL biopsies contained proportionally fewer but not statistically significant $CD3^+$ T lymphocytes ($P = .107$) but, as expected, markedly reduced $CD4^+$ ($P < .001$) and $FOXP3^+$ T cells ($P < .001$). As a result of CD4 depletion, $CD8^+$ T cells formed the predominant type of the T-cell infiltrate.

As a result of CD4 depletion, $CD8^+$ T cells formed the predominant type of the T-cell infiltrate. To identify tumor-infiltrating cytotoxic T lymphocytes (CTLs), we stained for TIA1, perforin, and granzyme B. Comparison of the 2 groups revealed a discrepancy in CTL highlighted by TIA1 and granzyme: TIA1 was more frequent among HIV-negative patients whereas granzyme expression was significantly higher in AR-DLBCL. The physiologic regulation of cytotoxic molecules may help explain this paradox: TIA1 is produced regardless of activation status while granzyme occurs in granules upon cell activation.

Historically, the median survival pre-HAART was <12 months, whereas after HAART it increased to 15 to 34 months. This improvement is mainly attributed to the restoration of cell-mediated immunity. In comparing the data between the 2 periods, they found higher numbers of $CD4^+$ T cells in HAART-era specimens ($P < .001$) whereas expression of other lymphocytic markers was not significantly different. Macrophages are a major target of HIV and a source of virus production. Additionally, tumor-associated macrophages play diverse and critical roles in tumorigenesis. We found no significant difference in the number of $CD68^+$ macrophages or in their proportion in tumor mass between HIV-infected and uninfected patients or between the 2 eras.
Our analysis revealed that the amount of neovasculature was strikingly higher in AR-DLBCL ($P < .001$ both for microvessels and sprouts) than in sporadic DLBCL.
The HIV-1 tat protein plays a central role in HIV-1 regulation by promoting the transcription of genes encoding structural proteins such as p24. Tat released from infected cells is notable for its ability to circulate in blood or to pass through cell membranes and cause deregulation of intracellular pathways in uninfected cells including endothelial cells and B cells

Hodgkin lymphoma

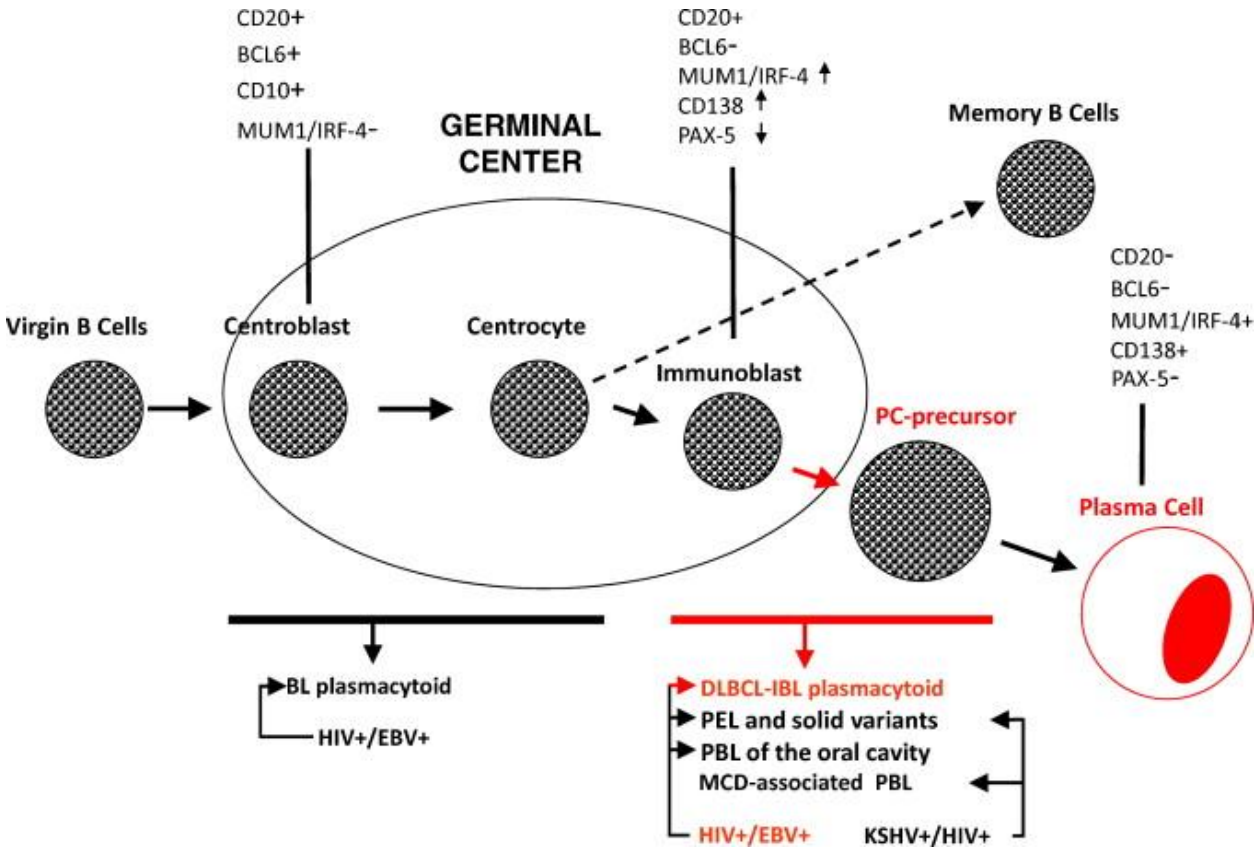
Although Hodgkin lymphoma (HL) is not considered an AIDS-defining malignancy, population-based studies have demonstrated an increased incidence of this disease in the setting of HIV infection. In a prospective cohort study of 11,112 individuals who were positive for HIV, with 71,687 patient-years of follow-up, the incidence of HL was 14 times higher than in the general population. In contrast to other HIV-associated malignancies that occur more commonly with severe immunocompromise, HL is associated with moderate immunologic impairment and the incidence actually seems to decline at CD4+ lymphocyte counts of less than 200/µL. Although incidence rates for the AIDS-defining malignancies (Kaposi's sarcoma, aggressive B-cell non-Hodgkin lymphoma [NHL]) have fallen, the incidence of HL may actually be increasing since the advent of combination antiretroviral therapy (cART), perhaps as a consequence of improvement in the level of immune function.

HL in the HIV-seropositive population is more likely to have mixed cellularity or lymphocyte-depleted histology and is almost always Epstein-Barr virus–associated. Before the introduction of cART, treatment outcomes for HIV-HL were poor.

Etiology and Pathogenesis

Lymphoma in HIV patients are hetereogenous, reflecting several pathogenetic mechanisms, chronic antigen stimulation, genetic abnormalities, cytokine deregulation, and the role of EBV and HHV8. However EBV positive lymphomas decreased in the HARRT era. HIV related lymphomas are consistently monoclonal and characterized by a number of genetic abnormalities of MYC and BCL6 genes as well as tumor suppressor genes. The recognition of a polyclonal or oligoclonalnature of some HIV related lymphoid proliferations suggest multistep lymphomagenesis. B cell stimulations, hypergammaglobulinemia and persistent generalized lymphadenopathy preceding the development of these lymphomas probably reflect the role of chronic antigenic stimulation.disruptions of the cytokine network leading to high serum levels of IL6 and IL 10 is a feature of HIV related lymphomas associated with EBV or HHV8. EBV is identified in the neoplastic cells of approximately 40% of HIV related lymphomasbut the detection of EBV varies considereably with the site of presentation and histological type..

From a histopathologic point of view, most lymphomas arising in HIV-seropositive individuals are characterized by a plasmablastic morphology. CD138 and MUM1, markers of post CG/terminal B-cell/plasmacytic differentiation, are useful in identifying the B-cell origin of all these tumors that show variable or negative expression of CD20 and CD79a.



Lymphomas specifically arising in HIV-infected patients. Important features to subclassify these neoplasms include the stage of differentiation of the putative cell of origin and its association with viruses. Lymphoma histotypes occurring specifically in HIV-infected patients exhibit a common normal cellular counterpart that may be defined as plasmablast. Abbreviations: DLBCL-IB, diffuse large B-cell lymphoma immunoblastic; EBV, Epstein–Barr virus; KSHV, Kaposi sarcoma herpesvirus; MCD, multicentric Castleman disease; PBL, plasmablastic lymphoma; PC, plasma cell; PEL, primary effusion lymphoma.

HIV and Hepatitis co infections

Hepatitis C

End-stage liver disease is the main cause of death in human immunodeficiency virus (HIV)/ hepatitis C virus (HCV)-coinfected patients under antiretroviral therapy. Liver fibrosis progresses fast among HIV/HCV-coinfected patients and, as a consequence, after the first decompensation patients die soon. However, financial restrictions have constrained treatment with telaprevir or boceprevir mostly to individuals with cirrhosis in some countries. In a recent a retrospective cohort study that included HIV-infected

patients, seen at eleven tertiary Spanish centers from November 1990 to June 2012, with HCV confection as determined by detectable plasma HCV RNA. Among them, individuals fulfilling the following criteria were selected: 1) No therapy against HCV infection during the follow-up or, if they received therapy against HCV infection during the follow-up, lack of SVR to that treatment; 2) Advanced fibrosis as determined by liver biopsy or liver stiffness measurement (LSM). Overall, 892 HIV-infected patients met the inclusion criteria for this cohort. Among individuals with baseline liver biopsy, 46 (14.5%, 95%CI: 10.8%-18.9%) patients died during the follow-up. Six (13%) deaths were due to AIDS, 24 (52%) were liver-related deaths and 16 (35%) were due to other causes.In the present study we found that HIV/HCV-coinfected patients with advanced fibrosis, but still without cirrhosis, are at risk of liver decompensations in the short-term, albeit the likelihood is lower than in individuals with cirrhosis. The first liver decompensations emerged as soon as one year after the detection of advanced fibrosis, either diagnosed by the observation of fibrosis stage 3 in liver biopsy or of a LSM ≥9.5 KPa and <14.6 KPa. Low platelet counts may have some utility to identify patients diagnosed of precirrhosis using LSM with an increased risk of decompositions. Experts or panels of experts have proposed immediate therapy with DAAs for patients with bridging fibrosis or cirrhosis.

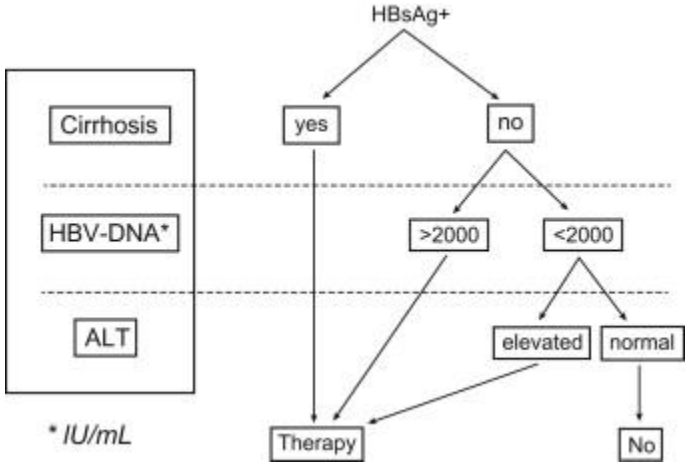
The herein reported study suggests that immediate therapy for chronic hepatitis C should be considered for HIV-infected patients with advanced fibrosis without cirrhosis. These patients are at risk of liver decompensations during the initial one to three years after diagnosis. The current usual practice of giving maximal priority to HIV/HCV genotype 1-coinfected patients with cirrhosis for combination therapy with telaprevir or boceprevir needs to be expanded to also include individuals with advanced fibrosis. Some experts have proposed to manage HIV/HCV genotype 1-coinfected patients with fibrosis stage 3 similarly as individuals with fibrosis stage 2, and differentiating them form subjects with cirrhosis.

Hepatitis B

The prevalence of chronic hepatitis B (CHB) in HIV patients varies between 4% and 10%. Most individuals exposed to HBV (≈85%) attain HBsAg seroconversion within the first 6 months, and develop HBcAb+ with or without HBsAb+. These patients have resolved, but not cured, HBV infection because integrated, episomal HBV-DNA remains in the hepatocytes. If the patient experiences potent immune suppression for any reason, HBV reactivation may occur.All HIV-infected persons must be tested for HBV markers of current (HBsAg+) or past infection (HBcAb+ with or without HBsAb+). Testing must be refreshed in patients with special features such as unexplained ALT elevations, visits or living in endemic areas, household contact with HBsAg+ persons, IDUs, multiple sexual contacts, history of sexually transmitted diseases, MSM, prison inmates, pregnant women, and chronic HCV individuals.HIV infection complicates the natural history of HBV, promoting higher rates of chronic cases following acute exposure, greater levels of HBV replication in chronic carriers, and diminished

incidences of spontaneous seroclearance of either HBV e antigen (HBeAg) and/or HBsAg. Overall, the incidence of cirrhosis and mortality attributable to HBV-related liver disease are significantly increased in HIV-coinfected patients compared with HBV-monoinfected individuals. A low CD4 cell count in HIV/HBV-coinfected patients has been associated with increased risk of cirrhosis and HCC. In Western countries, liver-related complications have become a leading cause of death in HIV-positive persons and chronic hepatitis B and/or C are the major contributors. In one European study, both all-cause and liver-related mortality were significantly increased among HIV/HBV-coinfected patients compared with HIV-monoinfected individuals.

Moreover, the presence of chronic HBV infection negatively impacts on HIV AIDS progression, enhancing HIV replication and pronouncing the loss of CD4 cells. Another obstacle that may compromise the success of antiretroviral therapy in HIV patients with concomitant chronic hepatitis B depends on its increased risk of antiretroviral-related hepatotoxicity



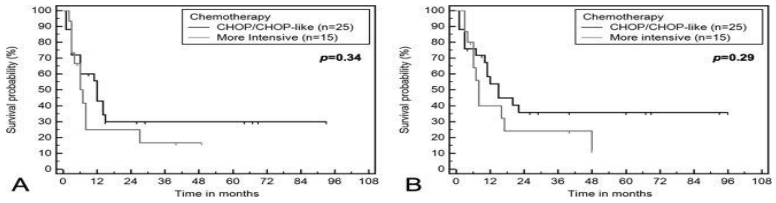
Treatment

In a recent multicenter/international study published on 50 patients**,** the median age was 43 years (range, 19-66 years). Twenty-one patients (43%) were receiving HAART at the time of PBL diagnosis. Chemotherapy was received by 85% of patients (n = 40), with 63% (n = 25) receiving cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and 37% (n = 15) receiving more intensive regimens (8 patients received infusional etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone [EPOCH]; 5 patients received hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [hyper-CVAD]; 1 patient received bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide [VDT-PACE]; and 1 patient received combined cyclophosphamide, vincristine, doxorubicin, and methotrexate plus ifosfamide, mesna, etoposide, and cytarabine [the Magrath regimen]). Radiotherapy was received by 6 patients (13%), mainly for palliative purposes, because 5 patients had stage IV disease. A minority of patients (n = 4; 10%)

underwent autologous hematopoietic stem cell transplantation (HSCT), including 1 patient as part of front-line treatment and 3 patients in the relapsed setting.

The median PFS and OS after diagnosis were 6 months and 11 months, respectively, and the estimated 5-year PFS and OS rates were 23% and 24%, respectively. Among the patients who received chemotherapy, obtaining a CR was associated with a median OS of 48 months compared with 3 months for patients who obtained less than a CR ($P < .001$). In the survival analyses, an ECOG performance status ≥2, advanced stage, and *MYC* rearrangement were associated with shorter median PFS and OS rates. A high/high-intermediate aaIPI score was associated with worse PFS and OS than a low/low-intermediate aaIPI score.

Human immunodeficiency virus-associated plasmablastic lymphoma



Cancer
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Castillo et al identified 112 published cases of PBL in HIV-positive patients from January 1st 1997 to December 31st 2007. Articles originated worldwide including North America ,, South America , Europe, Asia and Australia. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was the most commonly used therapeutic regimen (30%). Other chemotherapy regimens were used in 25% of the cases and included EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone) and CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine). Radiotherapy alone or in combination with cytotoxic chemotherapy was used in 29% of the cases. CNS prophylaxis with intrathecal methotrexate was reported in 9% of cases. Stage I patients were treated with chemotherapy in 54%, chemoradiotherapy in 27%, radiotherapy alone in 8%, and no therapy was given to 12% of the cases. Patients who presented with stage IV PBL received chemotherapy in 77% and chemoradiotherapy in 23% of the cases. Response

to therapy was reported in 35 patients, and 23 patients (66%) achieved a complete response to initial therapy. Despite this apparently good initial response, primary progressive disease was reported in 29% of cases, and the relapse rate was observed in 25% of the remaining cases. Finally, 53% of patients died, and 47% were alive with a median overall survival of 15 months from lymphoma diagnosis. Data on cause of death were available for 17 patients; the vast majority of these cases died from lymphoma (82%). Other causes of death were AIDS (12%) and sepsis (6%).

In a pooled analysis of sequentially performed trials for HIV-associated, aggressive B-cell NHL, they observed improved clinical outcomes for patients who received rituximab plus infusional EPOCH compared with rituximab plus standard CHOP chemotherapy, including significantly improved EFS and OS. Benefits were observed in both high-risk and low risk patients but were more pronounced in the high-risk IPI group.

Barta et al, did a pooled analysis, which included patients who received concurrent rituximab plus chemotherapy in AMC010 (R-CHOP) and AMC034 (R-EPOCH), were to determine whether the apparent benefit of infusional therapy persisted after adjustment of known prognostic covariates and to identify patients at high risk of lethal toxicity when receiving rituximab plus chemotherapy.

Characteristic	No. of Patients (%)		P
	AMC010: R-CHOP, N = 99	AMC034: R-EPOCH, N = 51	
Age: Mean±SD, y	43.5±8.3	42.6±8.4	.52
Men	90 (91)	43 (84)	.28
Age-adjusted IPI			
Low risk	41 (41)	16 (31)	
High risk	58 (59)	35 (69)	.29
Baseline CD4 count, /μL			
Median [range]	130 [1-2457]	181 [2-882]	.28[a]
<50	22 (22)	8 (16)	
<100	36 (36)[b]	16 (31)	
≥100	52 (52)[b]	35 (69)	
Histology			
DLBCL	80 (81)	35 (69)	.11
Other[c]	19 (19)	16 (31)	

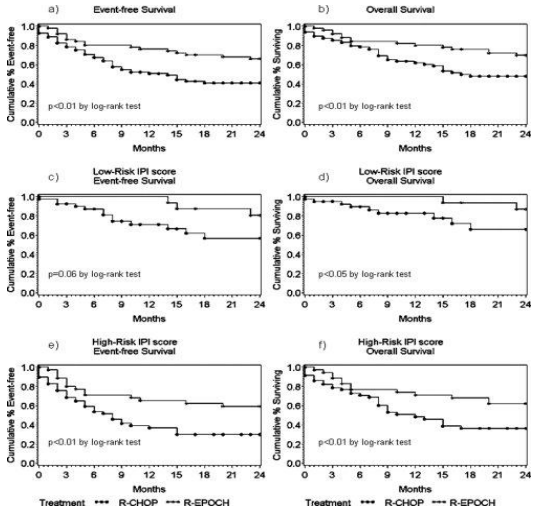
Abbreviations: AIDS, Acquired Immunodeficiency Syndrome; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; R-CHOP, rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisone; R-EPOCH, rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; SD, standard deviation.

a *P* values are for differences in the median CD4 count between the 2 groups.

b For 11 patients in AMC010, the baseline CD4 count was missing.

c Other lymphoma subtypes included the following: in AMC010, Burkitt lymphoma (n = 8; 8%); high-grade lymphoma, not otherwise specified (n = 4; 4%); polymorphic B-cell lymphoma (n = 2; 2%); and, in 1 patient each (1%), mixed histology, primary effusion, and missing; in AMC034, Burkitt/Burkitt-like lymphoma (n = 16; 31%).

Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma



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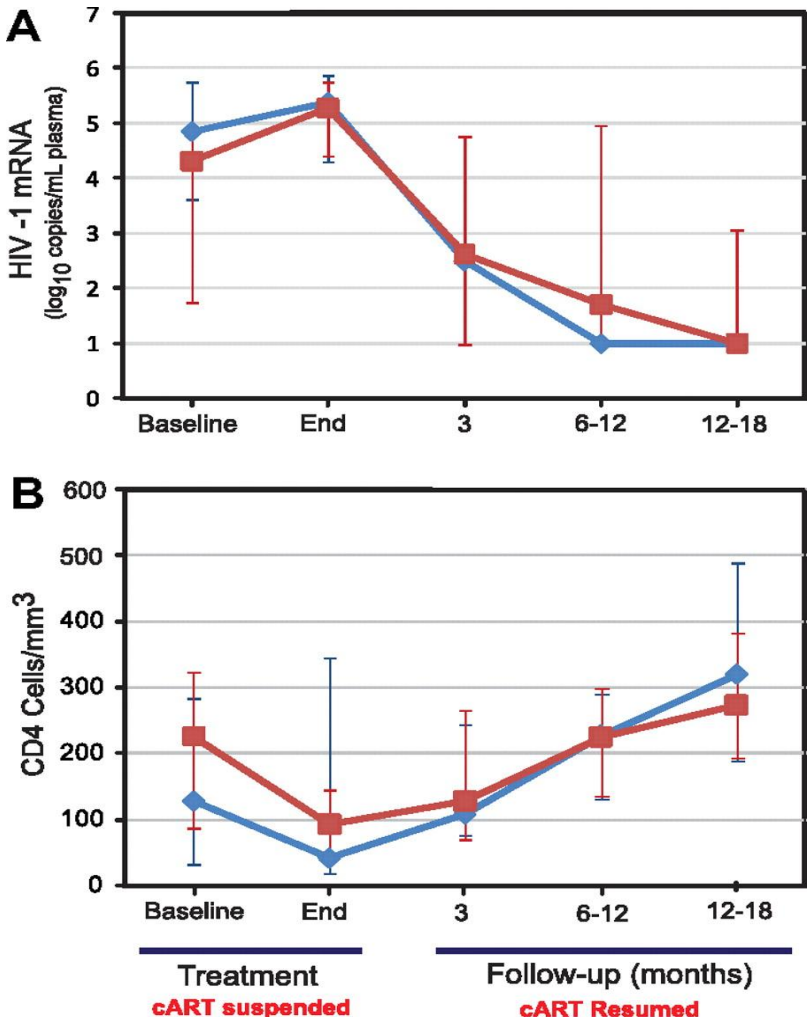
In a phase 2 study Dunleavy et al assessed the role of tumor histogenesis (subtype), fluorodeoxyglucose positron emission tomography (FDG-PET), and short-course etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin with dose-dense rituximab (SC-EPOCH-RR) in newly diagnosed HIV-associated $CD20^{+}$ diffuse large B-cell lymphoma. Patients received a minimum of 3 and a maximum of 6 cycles with 1 cycle beyond stable radiographic and FDG-PET scans. Overall, 79% of patients received 3 cycles. Combination antiretroviral therapy was suspended before and resumed after therapy. Thirty-three enrolled patients had a median age of 42 years (range, 9-61 years), and 76% had a high-intermediate or high age-adjusted international prognostic index. At 5 years median follow-up, progression-free and overall survival were 84% and 68%, respectively. There were no treatment-related deaths or new opportunistic infections during treatment, and patients had sustained CD4 cell count recovery and HIV viral control after treatment. FDG-PET after 2 cycles had an excellent negative but poor positive predictive value. Tumor histogenesis was the only characteristic associated with lymphoma-specific outcome with 95% of germinal center B-cell (GCB) versus 44% of non-GCB diffuse large B-cell lymphoma (DLBCL) progression-free at 5 years. SC-EPOCH-RR is highly effective and less immunosuppressive with shorter duration therapy compared with standard strategies.



HIV viral load and T-cell dynamics. (A) Median change in plasma mRNA HIV viral loads in 28 patients without early deaths. Viral loads increased with the peak shown at the end of therapy and declined below baseline at 3 months after completion of therapy and reinstitution of cART. cART-naive patients (♦) compared with patients with prior exposure (■) had slightly higher viral loads at presentation. (B) Median changes in CD4 cells in 28 patients without early deaths. CD4 cells declined to a nadir at end of therapy but recovered to baseline 6 to 12 months later. cART-naive patients (♦) compared with patients with prior exposure (■) had lower CD4 cells at baseline but equivalent CD4 cells 6 to 12 months after therapy. Medians with 95% CIs calculated by bootstrapping are shown.

Based on the above study most HIV-associated DLBCLs are curable with 3 cycles of SC-EPOCH-RR, and tumor histogenesis is the most important determinant of lymphoma-specific survival. Although FDG-PET is useful when used alongside CT

scans to determine when treatment is completed, they should be used with caution in HIV-associated DLBCL. These results suggest that SC-EPOCH-RR is an important advance for HIV-associated DLBCL, although AIDS-related deaths and non-GCB DLBCL remain important barriers to overall survival.

Primary CNS lymphoma

The long-term remission that was observed in this patient with PCNSL and HIV, who was treated with HAART alone, The clinical course of PCNSL is rapid, with a median survival of less than 2 months in untreated patients, and outcome is not significantly improved after the introduction of either conventional whole-brain radiotherapy (WBRT) followed by chemotherapy or WBRT without chemotherapy.

A recent study from Florida included Forty-one patients with positive HIV serology and 45 HIV-negative patients were included in the study. In the HIV-positive patients, the diagnosis was established by fulfillment of the following 3 clinical criteria: (1) compatible magnetic resonance (MRI) scan; (2) compatible positive SPECT thallium-201 study; (3) unresponsiveness to toxoplasmosis treatment or positive EBV-DNA PCR in CSF. Therapy was given at the discretion of the treating physician and varied between the patients. Radiotherapy (alone or combined with chemotherapy) was more frequently utilized in the HIV-negative group (68% vs. 27%, $P < 0.001$). Furthermore, HIV-negative patients were more likely to receive radiotherapy at doses above 36 Gy compared to HIV-positive patients (68% vs. 18%, $P = 0.005$). No clinical response was seen in 2 HIV-positive patients who received radiotherapy only. Chemotherapy was incorporated into the therapeutic approach in 27 (60%) HIV-negative and 25 (61%) HIV-positive patients. The most commonly used chemotherapy regimen in the HIV-negative group was methotrexate-based, following the DeAngelis protocol [, with an ORR of 73%. All 25 HIV-positive patients were treated with AZT combinations, with a cumulative ORR of 56%.

Overall response (OR) rates and overall survival (OS) achieved in HIV negative and positive patients according to the treatment modalities used

Treatment	n	OR	*P*	Median OS ± SE (mos)	*P*
WBRT only					
HIV−	11	6	NS	10.3 ± 4.5	
HIV+	2	0		Not calculated	
Chemotherapy only					
HIV−	7	4	NS	21.3 ± 8.5	NS
HIV+	16	9		4.0 ± 4.3	
WBRT + chemotherapy					
HIV−	20	14	NS	23.8 ± 9.7	0.001
HIV+	9	5		3.4 ± 1.5	
No treatment					
HIV−	7			1.0 ± 10.9	NS
HIV+	14			0.7 ± 0.3	

HIV− N = 45; HIV+ N = 41

SE standard error, *WBRT* whole brain radiotherapy

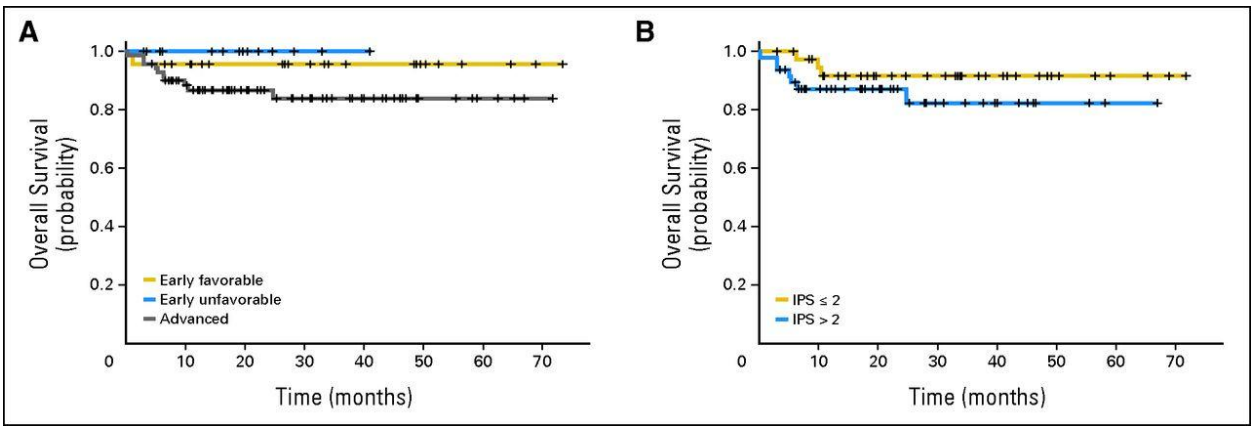
Chemotherapy regimens used: DeAngelis protocol, fludarabine + cytarabine, high dose methotrexate with or without temozolomide, Azidothymidine in combination with hydroxyurea or high dose methotrexate or high dose IL-2 + ganciclovir

In the combined cohort of the HIV negative and positive patients, shorter OS was associated with KPS < 70. In patients who were not on HAART before PCNSL diagnosis, initiation of HAART was associated with better OS (median (95% CI): 4.0 (3.1–4.8) vs. 1.1 (0.8–1.3) months, P = 0.007).

Hodgkin lymphoma

German HIV-Related Lymphoma Study Group presents data from the largest prospective trial ever conducted in patients with HIV-associated HL. In this study, 112 patients were allocated to treatment on the basis of stage and risk category. Those with early-stage favorable disease (IA/B or IIA/B) received two to four cycles of ABVD plus 30 Gy of involved-field radiotherapy. Patients with early-stage unfavorable disease received four cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) at baseline or four cycles of ABVD followed by 30 Gy of involved-field radiotherapy if disease was > 5 cm or residual disease was ≥ 2 cm. Those with advanced disease received eight cycles of BEACOPP with or without radiotherapy to sites > 2.5 cm. Patients with advanced HIV disease, including Eastern Cooperative Oncology Group performance score > 2, received ABVD. Of 108 patients (including eight female patients) included in the study, 23 (21%) had early favorable HL, 14 (13%) had early unfavorable HL, and 71 (66%) had advanced-stage HL. The median CD4 count at HL diagnosis was 240/μL. The complete remission rates for patients with early favorable, early unfavorable, and advanced-stage HL were 96%, 100%, and 86%, respectively. The 2-year progression-free survival of the entire study population was 91.7%. Eleven patients (11%) have died, and treatment-related

mortality was 5.6%. The 2-year overall survival rate was 90.7% with no significant difference between early favorable (95.7%), early unfavorable (100%), and advanced-stage HL (86.8%). In an Italian retrospective study of 114 patients with HIV-associated HL who received various standard chemotherapeutic regimens, the median OS was 15 months. Sixty percent died, 35% of those from opportunistic infection, 33% from HL, and 12% from both.



Take Home Messages

Incidence of HIV associated Lymphomas are declining.

Clinical outcome in African Americans are still poor compared to other races.

The most common Lymphoma associated with HIV is Diffuse large B cell lymphoma

Patients with Hepatitis B and C should be managed appropriately to prevent liver related complications

Patients with HIV associated Lymphomas should be treated with aggressive combination chemotherapies such as Dose adjusted EPOCH R and if treated adequately the outcome will as comparable to non HIV patients.

Addition of Rituximab has improved clinical outcome in HIV associated NHLs.

More clinical research needs to be done to improve the long term clinical outcome and racial disparities.

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