HIV Lymphoma

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Updates:

- Hodgkin's Disease

Introduction & Epidemiology

Patients with HIV infection are at a significantly increased risk of developing certain types of NHL compared to the general population. In the era of highly active antiretroviral therapy (HAART), a decline in lymphoma incidence has occurred, although, not to the same degree noted for other complications of HIV infection [1, 2]. As a result, lymphoma remains a common initial AIDS-defining illness in patients receiving HAART [2]. Risk factors for the development of NHL in this current era include lower CD4 count, higher HIV viral load, increased age and male gender [3]. The most recent CD4 count (as opposed to nadir count) is independently prognostic for development of lymphoma, suggesting a reduced risk of developing lymphoma if immune reconstitution with HAART occurs. Indeed, a recent prospective cohort study confirmed a reduced risk of NHL development with HAART exposure compared to single agent or no antiretroviral treatment [4].

Diagnosis & Pathology

The diagnosis of AIDS-related lymphomas is dependent on an adequate biopsy specimen (preferably an open surgical biopsy) with immunohistochemistry. Most AIDS-related lymphomas are intermediate or high-grade B-cell NHLs. Common subtypes include DLBCL/immunoblastic lymphoma, Burkitt and Burkitt-like lymphoma. The remainder of this treatment policy will address the management of these subtypes. AIDS-related lymphomas typically present in advanced stages of disease with frequent bone marrow and other extranodal involvement, bulky lymphadenopathy, and elevated lactate dehydrogenase [5]. Primary CNS lymphoma is a distinct extranodal presentation of DLBCL that is associated with EBV infection, severe immunosuppression ($CD4 < 50/mm^3$), and a poor median survival of 4 months [5]. Additional rare entities to be considered in the HIV setting include plasmablastic lymphoma of the oral cavity and primary effusion lymphoma.

Baseline Investigations

The following investigations are indicated for patients with intermediate or high-grade lymphoma in the setting of HIV infection:

- CBC and differential
- Serum electrolytes and renal function
- Liver profile
- LDH
- CT chest, abdomen and pelvis
- Total body gallium scan
- Unilateral bone marrow aspiration and biopsy
- CD4 count and viral load
- CMV serostatus
- Hepatitis B and C serologies
- CSF analysis

Patients who will be managed with palliative intent may have more limited staging investigations with a focus on identification of disease that is likely to require symptomatic management.

CSF analysis should be performed in all patients with AIDS-related lymphoma, given a high-rate of leptomeningeal involvement (10-20% at presentation) [6, 7] and propensity for CNS relapse [8, 9]. Samples should be sent for cell count, protein, and 10 cm^3 should be sent for cytology examination.

Cardiac assessment should be performed according to the guidelines in the DLBCL section.

Prognosis & Staging

Prognosis in AIDS-related lymphoma is related to the underlying severity of HIV infection and the extent of lymphomatous involvement. In an analysis of 192 patients enrolled in a phase III study (comparing low-dose m-BACOD to standard dose m-BACOD), the following factors had independent prognostic value: age > 35, stage III/IV disease, CD4 < 100/mm^3, and history of intravenous drug use [10]. The median survival was 46 weeks for patients with 0 or 1 risk factors, 44 weeks for patients with 2 risk factors, and 18 weeks for patients with 3 or more risk factors. An earlier report found that Karnofsky performance status < 70%, history of AIDS diagnosis, and bone marrow involvement were predictive for shorter survival, with a median survival of 4 months in patients with all 3 risk factors compared to 11.3 months in patients with no risk factors [11]. In addition, the age-adjusted IPI has been validated in HIV patients [12]:

Age-adjusted IPI (adapted from Rossi, Cancer 1999)

Risk Group	Distribution of cases	CR rate (%)	Median survival (mos)
Low	5 (7%)	100	>60 (not reached)
Low-intermediate	12 (17%)	88	17
High-intermediate	16 (23%)	50	10.9
High	36 (52%)	32	6.8

It should be emphasized that the above prognostic studies predate the routine use of HAART therapy. Recent evidence suggests that the outcomes for patients with HIV-related DLBCL are approaching those attained by HIV-negative patients. Moreover, in the HAART era, only increased IPI scores and failure to attain complete remission are associated with decreased survival, with CD4 count and other HIV-related parameters no longer retaining prognostic significance in the modern period [13].

Patients with AIDS-related lymphoma should be staged according to the Ann Arbor and IPI staging systems.

Stage Definition (see section on DLBCL)

Management

Chemotherapy and HAART

Survival of HIV patients in general has improved dramatically since HAART therapy became widely available in 1996 [14]. Large database studies of HIV patients with lymphoma have also suggested an improved survival in the post-HAART era compared to the pre-HAART time frame [5, 7], although conflicting data does exist [3, 15]. In a more recent German cohort study, a virologic response to HAART within 2 years following a lymphoma diagnosis was independently associated with improved overall survival [16]. This study suggested that the benefit of HAART was not an increase in response rate or lymphoma outcome, but an overall improvement in HIV-related mortality. Clearly, HAART plays an essential role in the prolongation of survival, but whether therapy needs to be administered concomitantly with or immediately after chemotherapy is still unclear.

Prior to the advent of HAART, patients with AIDS-related NHL were managed with lower-dose regimens due to concerns of unacceptable toxicity [17]. Survival at 2 years was approximately 10%. With the advent of HAART and anticipated restored immunity, more recent regimens have reported the use of standard dose chemotherapies without excessive toxicity.

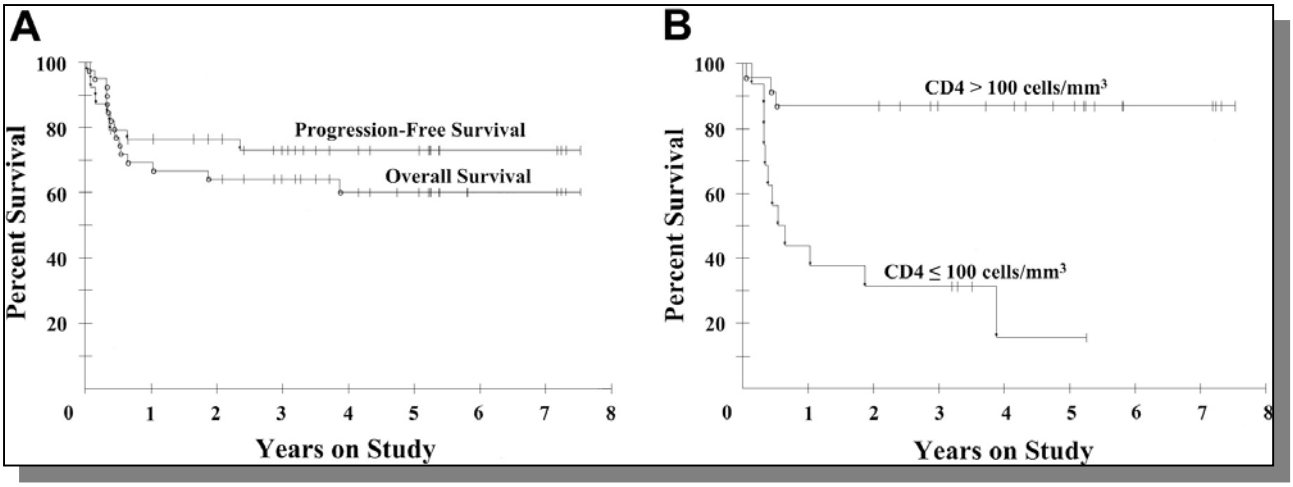
In 2001, the AIDS Malignancy Consortium [18] reported the feasibility of combining CHOP chemotherapy (dose-reduced or full dose CHOP with G-CSF) with concomitant HAART (stavudine, lamivudine, and indinavir) in 65 patients. Complete response rates were 30% and 48% in the reduced- and full-dose groups, respectively. Only one opportunistic infection (OI) occurred during chemotherapy administration. Cyclophosphamide clearance was reduced 1.5-fold compared to historical controls, without clinical significance. No long-term outcomes have been reported in this study. Other studies of CHOP-based chemotherapy and HAART have yielded median survival ranges from 21 months [5] to > 25 months (not yet reached after median follow-up of 9 months [19]).

More recently, a large multi-centre ECOG trial reported the efficacy of a 4-day infusional regimen (CDE) consisting of cyclophosphamide (200 mg/m^2/d), doxorubicin (12.5 mg/m^2/d), and etoposide (60 mg/m^2/d) repeated monthly [20]. Concurrent antiretroviral therapy was given in the form of didanosine (ddI) prior to 1996 (n=43 patients) and HAART thereafter (55 patients). Complete response rate (45%) and 2-year failure-free survival (36%) were similar in patients in the pre-HAART and HAART eras. However, overall survival at 2 years was improved in the era of HAART administration *(45% vs. 39%; p=0.039)*. Patients on HAART had fewer treatment-associated deaths compared to patients on ddI.

Therefore, HAART can be safely given with standard dose chemotherapy. Zidovudine should be avoided because of associated myelosuppression. Also, didanosine should be withheld because of possible worsening of peripheral neuropathy caused by vinca alkaloids [6].

Chemotherapy without HAART

Chemotherapy without concomitant HAART has also been studied. Reasons for HAART omission include concerns of drug-interactions with chemotherapy and inconsistent compliance with antiretrovirals resulting in increased resistance [6]. The NCI group described a dose-adjusted infusional regimen (DA-EPOCH) consisting of a 4-day infusion of etoposide (50 mg/m^2/d), vincristine (0.4 mg/m^2/d), and doxorubicin (10 mg/m^2/d), followed by an adjusted dose of cyclophosphamide according to initial CD4 count and subsequent nadir ANC (187-375 mg/m^2) and oral prednisone from days 1-5. Infusional therapy and dose-adjustment was felt to reduce the risk of multi-drug resistance and reduce toxicity. Thirty-nine patients were enrolled and HAART therapy was not administered until after the final cycle of chemotherapy. Median CD4 count was 198/mm^3 and 59% of patients were considered high or high-intermediate risk. A complete remission rate of 74% was achieved. Disease-free and overall survival after 56 months follow-up were impressive, 92% and 60%, respectively. During treatment, the median CD4 count fell 189 cells/mm^3, but returned to baseline by 6-12 months after completion of EPOCH. No opportunistic infections occurred during treatment, although 3 patients developed OIs within 2 months of completion of EPOCH.



These results suggest that immediate HAART therapy may not be necessary to attain a high CR rate. However, omission of HAART may be associated with higher toxicity [20] and risk of opportunistic infection during or immediately after chemotherapy [8]. No randomized data is available to guide decision making. In the absence of available clinical trials, we recommend that patients receive HAART concomitantly with chemotherapy (see below recommendations).

Rituximab

The AMC has also studied the role of rituximab therapy in patients with HIV-related lymphoma receiving concomitant HAART. Kaplan et al. reported a randomized trial of CHOP *versus* CHOP and rituximab (375 mg/m^2) given on day 1 of each cycle (for a total of 6-8 cycles) with an additional 3 monthly doses after CR was attained. CR rate with R-CHOP was similar to CHOP alone *(58% vs. 47%; p = NS)*, as was median overall survival *(139 weeks vs. 110 weeks; p = NS)*. There was a trend to decreased mortality from lymphoma in the R-CHOP group (14% vs. 29%). However, treatment with rituximab was associated with a statistically significant increased risk of death from infection *(14% vs. 2%; p = 0.035)*[21]. In the deaths with CD4 counts documented, 60% were in patients with CD4 < $50/mm^3$ and 40% occurred during the maintenance phase of rituximab. Smaller phase II studies of R-CHOP or infusional R-CDE have demonstrated higher CR rates (76-80%) without the same propensity for causing infectious complications [22, 23]. Until further clarified, it may be reasonable to withhold rituximab therapy.

G-CSF

The CCO and ASCO guidelines consider the use of G-CSF appropriate for secondary prophylaxis of neutropenic complications in patients treated with curative intent (CCO). Although primary prophylaxis with GCSF is frequently employed in studies of HIV-lymphomas [8, 17, 20], there is no clear demonstration of improved outcomes. However, ASCO guidelines do highlight the appropriateness of G-CSF use in the HIV setting, given the high likelihood of neutropenic complications and dose delay (ASCO).

Antibiotic Prophylaxis

Most clinical trials incorporate PCP [8, 18, 20] and/or fungal [20] prophylaxis into the treatment regimen, regardless of CD4 count. Discontinuation of the prophylaxis is reasonable with completion of treatment, unless required because of persistently low CD4 counts.

Limited Stage Lymphoma

Most patients with AIDS-related diffuse large B-cell lymphoma present with advanced disease. For the rare individuals with limited stage presentations, no data is available to guide optimal therapy. In the absence of trials, we suggest combined modality therapy analogous to the non-HIV setting (CHOP 3-6 cycles followed by involved-field radiation therapy). We recommend concurrent HAART therapy. The role of rituximab again is unclear; a reasonable approach is to withhold immunotherapy until the benefits of such treatment are further clarified.

Relapsed/Refractory Lymphoma

High dose therapy with stem cell support has been successful in carefully selected HIV patients with relapsed or refractory lymphoma. Ideally patients should have well-controlled HIV infection (viral load < 10,000 copies/mL and CD4 counts > 100). HAART therapy is feasible throughout the transplant process [24]. In one report of 20 patients (including 9 in first CR or PR), progression-free survival and overall survival were both 85% at a median follow-up of 32 months. Infectious complications were similar to those noted in the HIV-negative population and no long-term deterioration in immune function was found. Stem cell transplantation, ideally under an investigative protocol, should be considered in relapsed or refractory AIDS-lymphoma patients with good functional status and virologic control. For other patients, management could include other experimental protocols or palliation.

Burkitt and Burkitt-like Lymphoma (BL/BLL)

BL/BLL histologies usually make up 20-30% [8, 17, 20] of AIDS lymphoma cases enrolled in clinical trials. BL and variants are unique in that presentations can often occur at higher CD4 counts [6]. Prior to HAART, experience with dose-intense regimens was fairly limited, as most trials with BL/BLL patients excluded those with HIV (see BL section). Previously, studies of AIDS-related lymphomas combine DLBCL/immunoblastic and BL/BLL histologies, with no significant difference in outcome between the subtypes [6, 9, 25]. However, more recent research suggests that in the HAART era, treatment of HIV-BL with regimens used for DLBCL result in inferior outcomes [26]. Recent small retrospective studies (14-16 patients) reported the feasibility of using a dose-intensive B-ALL protocol or CODOX-M/IVAC with or without HAART, with acceptable response rates [27, 28]. Another small prospective study (13 patients) supported the use of Hyper-CVAD with a median survival of 12 months [29]. Unfortunately, there are no prospective studies demonstrating superior responses with high-dose compared to standard dose regimens [30]. In the absence of clear evidence defining the optimal management regimen for BL/BLL, we recommend the use of a dose-intense regimen (see BL policy) with concomitant HAART therapy in patients with good performance status and early HIV infection. For patients with end-stage AIDS or poor performance, a less intense approach (such as CHOP chemotherapy) can be considered.

Primary CNS Lymphoma (PCNSL)

PCNSL is more often associated with profound immunosuppression than the more common presentations of NHL noted above. Most patients present with CD4 count < 50 cells/mm^3. [5]. Radiologically, the appearance is of irregular ring-enhancing lesions, due to underlying extensive necrosis [31], with toxoplasmosis and progressive multifocal leukoencephalopathy figuring prominently in the differential diagnosis. Stereotactic brain biopsy is the standard for diagnosis. Whole-brain radiation (WBR) with corticosteroids was previously the cornerstone of management of AIDS-related PCNSL. Although responses occurred in up to 50% of patients, median survival was rarely beyond several months in duration [32]. Survival may be improved in the HAART era, with patients responding to HAART treatment demonstrating extended median survivals to beyond 1.5 years [33]. Smaller reports in this population have also shown responses to high-dose methotrexate (HDM) based regimens without the associated leukoencephalopathy of WBR. Jacomet found that 7 of 15 patients receiving HDM responded with a moderate median survival of 290 days [34]. No cognitive dysfunction occurred. Pilot studies have also suggested promise for therapy directed against EBV and HIV in the form of parenteral zidovudine, ganciclovir, and interleukin-2 along with HAART [35]. Although patients receiving this treatment have obtained prolonged remissions (> 22 months), data are still preliminary. In the absence of available trials, HDM-based chemotherapy is recommended at our Centre in patients who are fit for chemotherapy and who can be initiated on concomitant HAART treatment. Otherwise, patients should be palliated with WBR and corticosteroids.

Hodgkin's Disease

In the HAART era, the incidence of HD may be increasing [36], particularly in individuals with reconstituted immune systems (CD4 count > 200). It is hypothesized that the reconstituted immunity is necessary to generate the cytokine and inflammatory milieu needed to support the malignant potential of Reed-Sternberg cells [37]. Most patients with HIV-related HD present with advanced stage disease, B symptoms, extranodal involvement and bone marrow infiltration [9]. Standard dosing of ABVD has been studied prior to the advent of HAART, with significant toxicity and short remissions [38]. However, outcomes are expected to improve and treatment analogous to the non-HIV setting is currently recommended. Vigilance for increased vinca-associated neuropathy is warranted in those individuals who are concomitantly on protease-inhibitor based HAART, given the possibility of impaired vinblastine detoxification (mediated by CYP3A4) [39].

Recommendations

(1) Chemotherapy

- Patients with AIDS-related lymphomas should ideally be enrolled in clinical trials, if available. Patients who are treated off study should receive CHOP x 6-8 cycles (or 2 cycles beyond achievement of a complete response). Those with Burkitt/BLL histology should be treated with the Magrath regimen.
- Rituximab should be withheld pending further clarification of infectious risk.
- G-CSF for primary prophylaxis is reasonable if available. G-CSF for secondary prophylaxis is strongly recommended.
- CNS prophylaxis with cytarabine (50 mg IT weekly for the first 4 weeks of treatment) [18] or an appropriate alternative should be administered to all patients [6].
- PCP prophylaxis (trimethoprim-sulfamethoxazole 160 mg/800 mg p.o. three times weekly or an alternative) should be given to all patients. Patients with pre-existing of persistent neutropenia can have dapsone or aerosolized pentamidine substituted for trimethoprim-sulfamethoxazole. Fluconazole prophylaxis (100 mg po od) is also recommended [9].
- Patients who are CMV negative should receive CMV serology negative blood products if needed.

(2) HAART (as per AMC protocol)

- Patients who are treated off study should receive concomitant HAART therapy.
- Patients should be referred to an HIV specialist for appropriate selection of an antiretroviral regimen. An up-to-date evidence-based guideline for initiation and selection of therapy is maintained by the National Institute of Health **(www.hivatis.org)**
- Zidovudine should be avoided because of associated myelosuppression. Didanosine, stavudine, and zalcitabine may worsen vincristine-associated neuropathy, and should be used with caution.

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