Non-Hodgkin’s Lymphomas

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NCCN.org
AIDS-Related B-Cell Lymphomas
DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis
  - IHC panel: CD45 (LCA), CD20, CD3, CD10, BCL2, BCL6, Ki-67, CD138, kappa/lambda, HHV8
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20
- Epstein-Barr virus in situ hybridization (EBER-ISH)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish lymphoma subtype
  - DLBCL, Burkitt, Plasmablastic, Primary effusion lymphoma (PEL):
    - CD10, BCL2, Ki-67, BCL6, CD138, CD30 for PEL, KSHV LANA-1
- Molecular analysis to detect: antigen receptor gene rearrangements; BCL2; BCL6; MYC rearrangements
- Cytogenetics or FISH: BCL2; BCL6; MYC

See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
WORKUP

ESSENTIAL
- Physical exam: attention to node-bearing areas, including Waldeyer’s ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid, phosphate
- Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET-CT scan
- Bone marrow biopsy ± aspirate
- CD4 count
- Lumbar puncture, except for primary effusion lymphoma (PEL) and early-stage DLBCL
- HIV viral load
- Hepatitis B testing b
- Hepatitis C testing c
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- UGI/barium enema/endoscopy
- Neck CT
- Plain bone radiographs and bone scan
- Discussion of fertility issues and sperm banking
- Beta-2-microglobulin
- Brain MRI with gadolinium, or head CT
- EBV viral load
- Quantitative immunoglobulins

b Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

c Hepatitis C antibody and if positive, viral load and consult with hepatologist.

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**TREATMENT**

Antiretrovirals can be administered safely with chemotherapy, but consider changing (highly active antiretroviral therapy (HAART) to non-protease inhibitor-based or CYP3A4-neutral regimen to minimize interactions with chemotherapy. Any change in antiretroviral therapy should be done in consultation with HIV specialist. Concurrent HAART is associated with higher CR rates (Barta et al. Blood 2013,122:3251-3262).

### Burkitt lymphoma

- **Suggested regimens:**
  - CDE (cyclophosphamide, doxorubicin, etoposide) + rituximab
  - CODOX-M/IVAC (modified): cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine ± rituximab
  - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
  - If CD4 <50, benefit of rituximab less clear due to increased infectious complications
  - GCSF for all patients

### Diffuse large B-cell lymphoma

- **Suggested regimens:**
  - Dose-adjusted EPOCH + rituximab (preferred)
  - CDE + rituximab
  - CHOP + rituximab
  - GCSF for all patients

### Lymphoma associated with Castleman’s disease

- Intrathecal therapy (IT)†
  - If CD20-, rituximab is not indicated
  - If CD4 <50, benefit of rituximab less clear due to increased infectious complications

### Primary effusion lymphoma

- **Suggested regimens:**
  - Dose-adjusted EPOCH + rituximab (preferred)
  - CDE + rituximab
  - CHOP + rituximab
  - GCSF for all patients

For relapse, see **BCEL-6**

Consider prophylaxis for tumor lysis syndrome (**See NHODG-B**)  
See monoclonal antibody and viral reactivation (**NHODG-B**)

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*d* See **Supportive Care (AIDS-A).**  
*e* See references for regimens (**AIDS-B).**  
†Prophylactic IT methotrexate is used at some NCCN Member Institutions for all patients with HIV-associated DLBCL. At other NCCN Member Institutions, patients receive IT methotrexate in selective settings (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, EBER positivity, or ≥2 extranodal sites and elevated LDH).

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TREATMENT

Antiretrovirals can be administered safely with chemotherapy, but consider changing HAART to non-protease inhibitor-based or CYP3A4-neutral regimen to minimize interactions with chemotherapy. Any change in antiretroviral therapy should be done in consultation with HIV specialist. Concurrent HAART is associated with higher CR rates (Barta et al. Blood 2013,122:3251-3262).

**Plasmablastic lymphoma**

- Suggested regimens:
  - CODOX-M/IVAC (modified)
  - Dose-adjusted EPOCH
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine)
- Standard CHOP is not adequate therapy

**Primary CNS lymphoma**

- Initiate HAART, if not already receiving
- Even with poorly controlled HIV and/or marginal performance status, consider high-dose methotrexate
- For select patients with good performance status on HAART, see NCCN Guidelines for CNS- Primary CNS Lymphoma
- Consider RT alone for palliation of patients who are not candidates for systemic therapy
- Best supportive care (See NCCN Guidelines for Palliative Care)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

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See Supportive Care (AIDS-A).

See references for regimens (AIDS-B).

Management can also apply to HIV-negative plasmablastic lymphoma.

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SUPPORTIVE CARE

- Increased risk of infectious complications mitigated with improved HIV control and aggressive infection prophylaxis:
  - Patients not on HAART at diagnosis may initiate HAART during staging period, or alternately initiate after first cycle of chemotherapy. All HAART initiation or changes should be done in consultation with an HIV specialist.
  - AZT and non-boosted doses of ritonavir should not be administered concurrently due to myelosuppression.
  - While feasible to administer most protease inhibitors concurrently with chemotherapy, consideration of changing to non-protease inhibitor based regimens is helpful to avoid potential interactions affecting either chemotherapy or antiretroviral metabolism.

- Required for all:
  - Growth factor support: begin 24–48 hours after chemotherapy and continue past nadir recovery of blood counts of each cycle
  - PCP: Continue until CD4 recovered to >200 post completion of chemotherapy
  - Gram-negative rods: Quinolone prophylaxis or equivalent during period of neutropenia
  - Fungal: Azole antifungals should be held 24 hours prior to through 24 hours post chemotherapy with CYP3A4 metabolism
  - MAC prophylaxis for CD4<100

- Strongly consider VZV/HSV prophylaxis
- Strongly encourage consultation with infectious disease specialist for febrile neutropenia in context of extensive prophylaxis as well as for refractory diarrhea.
SUGGESTED TREATMENT REGIMENS

CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate alternating with ifosfamide, etoposide, high-dose cytarabine) ± rituximab

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)

Dose-adjusted EPOCH + rituximab

CDE (cyclophosphamide, doxorubicin, and etoposide)

CDE + rituximab

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) ± rituximab

CHOP + rituximab

Rituximab and CD4 counts

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AIDS-Related B-Cell Lymphoma

Overview

AIDS-related lymphoma is usually an AIDS-defining diagnosis in patients infected by the human immunodeficiency virus (HIV). Systemic lymphoma accounts for 70% to 90% of cases of HIV-associated lymphoma, while primary CNS lymphoma accounts for the remaining 10% to 30% of cases.\textsuperscript{1-3} The distribution of systemic versus primary CNS lymphoma (PCNSL) may vary depending upon differences in factors such as geographic regions, time period covered and referral patterns of the institutions, between published reports. Burkitt lymphoma (BL) and diffuse large B-cell lymphomas (DLBCL) are the most common forms of systemic HIV-associated lymphoma.\textsuperscript{2,3} In systemic cases of HIV-associated lymphomas, the BL histology is generally associated with a higher CD4+ cell count at diagnosis compared with DLBCL; cases of PCNSL is associated with much lower CD4+ count levels relative to systemic cases.\textsuperscript{1,2}

Prior to the development of highly active antiretroviral therapy (HAART), HIV-associated lymphomas often presented with widespread, extra nodal disease, B symptoms, CNS involvement, and poor prognosis.\textsuperscript{3} With the routine use of combination antiviral therapy in the HAART era, the prognosis of patients diagnosed with HIV-related NHL has improved, primarily for those with systemic lymphomas. In an early assessment of the shift in prognosis of patients with HIV-associated lymphomas between the pre-HAART (1993-1994) and HAART (1997-1998) eras, median overall survival (OS) improved from approximately 6 months in the pre-HAART years compared with 21 months in the HAART era for patients with systemic lymphomas; patients with PCNSL, however, continued to have poor prognosis, with a median OS less than 3 months during both periods.\textsuperscript{2} In a recent report from the COHERE (Collaboration of Observational HIV Epidemiological Research Europe) study evaluating outcomes of patients with HIV-associated lymphomas treated in the HAART era (1998-2006), the 1-year OS rates among patients with systemic lymphoma and PCNSL were 66% and 54%, respectively.\textsuperscript{1} Although survival outcomes appear to be improving with contemporary therapies, outcomes for patients with PCNSL remain poor. Moreover, survival rates for patients with HIV-associated lymphomas remain low compared with patients with lymphomas unassociated with HIV infection; in a recent study, the 2-year OS rate for patients with HIV-associated lymphomas treated in the HAART era (1996-2005) was 41% compared with 70% in lymphoma patients without HIV infections.\textsuperscript{4} Studies suggest that the improvement in prognosis observed with systemic HIV-associated lymphoma apply primarily to HIV-associated DLBCL but less to BL histology. In a study that investigated differences in outcomes by lymphoma histology and treatment era, median OS improved from 8 months (pre-HAART years: 1982-1996) to 38 months (HAART years: 1997-2003) among patients with HIV-associated DLBCL; contrastingly, OS outcomes remained poor (median 6 months to 5 months) during the same period among patients with HIV-associated BL.\textsuperscript{5} BL histology appears to be associated with poorer survival outcomes among patients with HIV-associated lymphoma, even in the HAART era.\textsuperscript{4,5}

Plasmablastic lymphoma (PBL) and primary effusion lymphoma (PEL) are two forms of lymphoma seen more commonly associated with HIV compared to lymphoma in patients without HIV infections. PEL accounts for less than 5% of HIV-associated lymphoma cases, most often occurring in the pleural, pericardial, and abdominal cavities.\textsuperscript{6,7} PELs are associated with human herpes virus 8 (HHV8) infection and
many are also co-infected with Epstein Barr virus (EBV). PBL is another unique large B-cell lymphoma that mainly involves the jaw and oral cavity of HIV-infected patients. Multicentric Castleman’s disease (MCD) is prevalent in HIV-infected individuals, and has also been associated with HHV8 infection and increased incidence of lymphoma in HIV infected patients.

**Discussion**

The diagnostic evaluation of HIV-associated lymphoma is not different from the non-HIV-associated disease. The major factor is to distinguish between BL and DLBCL. Hodgkin lymphoma and indolent lymphoma are seen in patients with HIV infection at an incidence higher than in the general population, but are much less common than BL or DLBCL.

**Workup**

The diagnostic evaluation and workup are as outlined in the NCCN Guidelines section for BL. However, all patients (without regard to histology) should have a lumbar puncture to rule out CNS involvement. In addition, baseline values for CD4 counts and HIV viral load should be obtained.

**Treatment**

Optimal management of HIV-associated lymphoma is not established. However, several key factors have emerged as being important to improve outcome. In general, studies have demonstrated that early introduction of HAART therapy is associated with superior outcomes. This has allowed for the administration of more dose-intense chemotherapy regimens and a reduction in treatment-associated toxicity.

In prospective phase II studies, combination chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CDE (cyclophosphamide, doxorubicin and etoposide) given with concomitant HAART have proven to be active and tolerable in patients with HIV-associated lymphoma. The CHOP regimen has been shown to induce CR rates of 30% to 48%, with a median OS of approximately 25 months in patients with HIV-associated lymphomas. The CDE regimen from the ECOG 1494 study demonstrated a CR rate of 45% with a 2-year OS of 43% in patients with HIV-associated lymphomas. In a phase I/II study, combination therapy with CDOP (cyclophosphamide, liposomal doxorubicin, vincristine and prednisone) given with concomitant HAART showed high response rates (88% overall) in patients with HIV-associated lymphoma (N=24; DLBCL or variant in 79% of patients). Liposomal doxorubicin was given at doses ranging from 40 to 80 mg/m², with fixed doses of the other three drugs. The CR rate with this regimen was 75%, and the median duration of CR was 16+ months; the OS rate at 1 year after start of therapy was 58%. Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) is another combination chemotherapy regimen that has been evaluated in patients with HIV-associated lymphoma. In a phase II study in previously untreated patients with HIV-associated NHL (N=39; 79% DLBCL; 18% BL), treatment with dose-adjusted EPOCH resulted in an ORR of 87% with a CR in 74% of patients. At a median follow up of 53 months, progression-free survival (PFS) and OS rates were 73% and 60%, respectively. Only 2 of the patients with a CR experienced disease recurrence at last follow up (for a disease-free survival [DFS] rate of 92%). OS outcomes were decreased among the patients with low baseline CD4 counts (< 100/mcL) compared with those with higher CD4 counts (16% vs. 87%). Multivariate analysis using a Cox
A proportional hazard model showed that low CD4 counts and CNS involvement were the only significant factors associated with decreased OS. With the advent and wide availability of the anti-CD20 monoclonal antibody rituximab, the safety and efficacy of this immunotherapy agent in combination with chemotherapy has also been evaluated in clinical trials for patients with HIV-associated lymphomas. In the randomized phase III trial conducted by the AIDS Malignancies Consortium (AMC 010 study) in patients with HIV-associated NHL (N=150; 80% DLBCL; 9% BL), the addition of rituximab to CHOP (R-CHOP) was associated with improved CR rates (CR + unconfirmed CR [CRu]) compared with CHOP alone (58% vs. 47%); the median PFS was similar between treatment groups (10 months vs. 9 months) but both the median time to progression (29 months vs. 20 months) and OS (32 months vs. 25 months) were longer with R-CHOP. These outcomes were not significantly different between treatment arms, however, and the R-CHOP combination was associated with increased risks of serious infections (including infection-related deaths in 14% of patients), particularly in patients with CD4+ counts of less than 50/mcL. It should also be noted that in this study, 35 patients randomized to the R-CHOP arm had received maintenance rituximab following initial R-CHOP. In subsequent phase II trials, 6 cycles of the R-CHOP regimen showed CR/CRu rates of 69% to 77% in patients with HIV-associated NHL (majority with DLBCL histology), with manageable toxicities. Infection-related deaths (regardless of attribution to study treatment) were reported in 2% to 9% of patients on these studies. In one study, the 2-year OS rate was 75%. In the other study, the 3-year OS rate was 56% and the 3-year DFS rate among patients with a CR (measured from the time of documented CR) was 77%. Rituximab in combination with infusional CDE (R-CDE) was also shown to be feasible and effective with an acceptable toxicity level in patients with HIV-associated lymphomas. In a phase II study in patients with primarily HIV-associated DLBCL histology (N=74; 72% DLBCL; 28% BL), the CR rate with R-CDE was 70% with a 5-year OS rate of 56% and time-to-treatment-failure rate of 52%; among patients with a CR (measured from the time of documented CR), the 5-year DFS rate was 81%. Infection-related deaths occurred in 8% of patients; 3% were considered related to study treatment. Rituximab was also evaluated in combination with infusional CDOP (R-CDOP) with concomitant antiretroviral therapy in a recent multicenter phase II trial (AMC 047 study) in patients with HIV-associated NHL (N=40; DLBCL in 98% of cases). The ORR was 67.5% with a CR in 47.5%. The 1-year PFS and OS rates were 61% and 70%, respectively; the 2-year PFS and OS were 52% and 62%, respectively. Infectious complications were reported in 40% of patients (grade 4 in 5%) but no infection-related deaths occurred. This may in part be explained by the fact that patients received concomitant HAART and those with low CD4 counts (≤ 100/mcL at baseline or during anti-tumor therapy) received antimicrobial prophylaxis. Factors such as decreased CD4 counts or increased HIV viral load did not appear to influence treatment response. These results with the R-CDOP regimen, however, appeared less favorable compared with the EPOCH regimen discussed earlier (74% CR; 60% OS at median 53 months follow up) or the EPOCH-R regimen (91% CR; 68% OS at median 5 years follow up), discussed below. The CODOX-M/IVAC regimen (cyclophosphamide, doxorubicin and high-dose methotrexate, alternating with ifosfamide, etoposide and high-dose cytarabine) with or without rituximab, is commonly used in the management of patients with BL. Retrospective studies suggest that this regimen may be applicable in patients with HIV-associated BL cases. In a small retrospective analysis that included a subgroup of patients with HIV-associated BL treated with CODOX-M/IVAC (n=8),
the CR rate was 63% with a 2-year event-free survival rate of 60%. In a recent retrospective study of CODOX-M/IVAC with or without rituximab in patients with BL (N=80), similar outcomes were observed between the subgroup of patients with HIV infection (n=14) and those without HIV infection (n=66). The CR rates among patients with and without HIV infection were 93% and 88%, respectively; the 3-year PFS rate was 68% for both subgroups, and the 3-year OS rate was 68% and 72%, respectively. This retrospective analysis also suggested that in the overall patient cohort, no significant differences in outcomes were observed with the addition of rituximab to CODOX-M/IVAC, although a trend toward improved 3-year PFS rate (74% vs. 61%) and OS rate (77% vs. 66%) with the addition of rituximab was noted. Among the small subgroup of patients with HIV-associated BL who received CODOX-M/IVAC with rituximab (n=10), 1 patient (10%) died due to a treatment-related infectious complication.

The EPOCH regimen in combination with rituximab (EPOCH-R) has been shown to be effective and tolerable in patients with HIV-associated lymphomas. In a study of dose-adjusted EPOCH with rituximab (DA-EPOCH-R) in patients with BL (N=23; including HIV-associated BL, n=8), the CR rate was 100% and both the PFS and OS rates at median 27 months of follow up was 100%. More recently, the EPOCH-R regimen was evaluated using a short course of EPOCH with dose-dense rituximab in patients with HIV-associated DLBCL (N=33). The CR rate with this regimen was 91%, and the PFS and OS rates were 84% and 68%, respectively, at a median follow up of 5 years. In this study, the addition of rituximab did not appear to cause serious infection-related complications or deaths. The AMC 034 randomized trial evaluated the use of the EPOCH regimen in combination with sequential versus concurrent rituximab in patients with HIV-associated lymphomas (N=106; 75% DLBCL; 25% BL, BL-like). The CR rate was 73% and 55% of patients in the concurrent (n=48 evaluable) and sequential (n=53 evaluable) arms, respectively; the 2-year PFS rate (66% vs. 63%) and OS rate (70% vs. 67%) were similar between treatment arms. Toxicity was comparable in the 2 treatment arms, although the concurrent regimen was associated with a higher incidence of treatment-related deaths among the patients with a baseline CD4+ count of less than 50/mcL. Overall, treatment-related deaths occurred in 5 patients (10%) in the concurrent arm (n=3 due to infections) and 4 patients (7%) in the sequential arm (n=3 due to infections). The authors concluded that concurrent EPOCH-R was an effective regimen for HIV-associated lymphoma, which merits further evaluation. The investigators from the aforementioned AMC trials (AMC 010 and AMC 034) recently conducted a pooled analysis that included patients with HIV-associated NHL treated in the R-CHOP or EPOCH-R protocols (N=150 total). The analysis was intended to evaluate patient/disease factors and treatment factors associated with outcomes. Factors such as low age-adjusted IPI score and baseline CD4 count 100/mcL or greater were significantly associated with improved CR rate, EFS and OS outcomes. Among the patients who were treated with concurrent EPOCH-R, both EFS and OS were significantly improved compared with R-CHOP (after adjusting for aaIPI and CD4 counts). The incidence of treatment-related deaths were higher in patients with low baseline CD4 counts (<50/mcL) compared with those with higher CD4 counts (37% vs. 6%; \(P<0.01\)). The hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine) with or without rituximab has also demonstrated high CR rates (64–92%) and a median OS of 12 months in patients with HIV-associated BL/leukemia and Burkitt-like lymphoma.

The treatment of relapsed or refractory HIV-associated lymphomas remains a challenge, with autologous HSCT being the only potentially
curative strategy, a recent retrospective analysis evaluated outcomes in patients with relapsed or refractory HIV-associated lymphoma treated with curative intent at AMC sites (13 sites, N=88). The lymphoma diagnosis was NHL in the majority of patients (89%; the remainder had Hodgkin lymphoma [HL]). The most commonly used second-line regimens were ICE (ifosfamide, carboplatin and etoposide, 39%), dose adjusted EPOCH (19%) and ESHAP (etoposide, methylprednisone, cytarabine and cisplatin, 12.5%). Among the subgroup of patients with NHL, the ORR was 31% and the 1-year OS rate was 37%. Patients with a BL histology (n=12) appeared to have the worse outcomes with an ORR of 17% (compared with 33% in non-BL NHL) and a 1-year OS rate of only 12% (compared with 41.5% in non-BL NHL; \( P=0.005 \)). Among all patients (both NHL and HL), those with primary refractory disease (n=54) had significantly decreased ORR (24% vs. 56%; \( P=0.003 \)) and decreased 1-year OS (31% vs. 59%; \( P=0.022 \)) compared with those with relapsed disease. Baseline CD4 counts did not influence OS outcomes. Subsequent treatment with autologous HSCT was associated with improved 1-year OS (63% vs. 37%) compared with no transplant. However, for patients who experienced a response (CR or PR) after second-line therapy, no difference in 1-year OS was observed based on HSCT (87.5% with HSCT vs. 82% with no transplant). For patients with relapsed/refractory HIV-associated NHL who can tolerate curative treatment regimens, autologous HSCT may offer the best chance for disease control. Although this retrospective analysis suggests that some patients may experience durable remission without HSCT, longer follow up data are needed.

PBL was associated with a poor prognosis in the pre-HAART era. In the HAART era, prognosis has improved with the use of intensive chemotherapy regimens along with HAART. The outcome of the HIV-positive patients with PBL treated at the Memorial Sloan-Kettering Cancer Center was reported to compare favorably to reports in the literature. Among 6 patients treated with anthracycline-based multiagent chemotherapy in conjunction with HAART, 5 patients were alive and diseases free with a median follow-up of 22 months. However, only limited data exist on the treatment approach for patients with PBL.

PCNSL is associated with severe immunosuppression and an overall poor prognosis. In retrospective analyses, patients with PCNSL treated with HAART and RT had a more favorable outcome.

**NCCN Recommendations**

The NCCN Guidelines recommend the use of HAART and growth factor (e.g., G-CSF) support along with full-dose chemotherapy regimens. Any change in antiviral therapy should be made in consultation with an infectious disease specialist. Patients on antiretrovirals with persistently low CD4+ count of less than 50 to 100/mcL tend to have a poorer prognosis and higher risk of infection when being treated with rituximab-containing regimens. Therefore, omission of rituximab is strongly suggested for these patients due to the higher risk of serious infectious complications. CNS prophylaxis with intrathecal methotrexate is used at some NCCN institutions for all patients, whereas at other NCCN institutions, only the patients with HIV-associated DLBCL with selected high-risk features (e.g., involvement of 2 or more extranodal sites with elevated LDH, bone marrow involvement, or other high-risk site involvement such as epidural, testicular or paranasal sinuses) receive upfront prophylaxis.

Recommended treatment regimens for patients with HIV-associated BL include dose-adjusted EPOCH with rituximab (DA-EPOCH-R), CODOX-M/IVAC (with or without rituximab), CDE with rituximab, or
hyper-CVAD with rituximab. Recommended treatment options for patients with HIV-associated DLBCL include rituximab in combination with chemotherapy regimens such as dose-adjusted EPOCH, CDE or CHOP. The panel recommended DA-EPOCH-R as the preferred regimen for the treatment of HIV-associated BL and DLBCL. Patients with lymphoma associated with MCD and PEL can also be treated with the same regimens as described for patients with DLBCL. Since most cases of PEL are CD20-negative, the addition of rituximab to the chemotherapy regimen is not indicated.

The NCCN Guidelines recommend CODOX-M/IVAC, EPOCH or hyper-CVAD regimens for patients with PBL, with the realization that only limited data are available on the management of these patients at this time. High-dose methotrexate, RT or antiretroviral therapy can be considered for patients with PCNSL. Selected patients with good performance status receiving HAART may also be treated as per the NCCN Guidelines for Primary CNS Lymphoma.
References


