AIDS-Related B-Cell Lymphomas

Note: Consider Clinical Trials as treatment options for eligible patients.

DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one tumor paraffin block. Rebiopsy if consult material is non-diagnostic.
- Adequate immunophenotyping to confirm diagnosis
  - Paraffin panel: CD3, CD10, CD20, CD45 (LCA), BCL2, BCL6, Ki-67, CD 138, kappa/lambda light chains, HHV8
  - Flow cytometry immunophenotyping (optional if paraffin IHC has been performed): kappa/lambda light chains, CD3, CD5, CD10, CD19, CD20, CD45
- In situ hybridization: EBER

OF USE IN CERTAIN CIRCUMSTANCES:

- Additional immunohistochemical studies to establish lymphoma subtype
  - Diffuse large B-cell, Burkitt, plasmablastic, primary effusion lymphoma: CD10, BCL2, Ki-67, BCL6, CD138, CD30 for PEL, KSHV LANA-1
- Molecular genetic analysis
  - FISH to detect *MYC*, BCL2 and BCL6 gene rearrangements

STRONGLY RECOMMENDED:

- FNA or core biopsy for tissue banking by protocol
- Perform gene mutation panel if available

INITIAL EVALUATION

ESSENTIAL:

- Physical exam:
  - Performance status (ECOG)
  - B symptoms (unexplained fever > 38°C during the previous month; Recurrent drenching night sweats during the previous month; Weight loss > 10 percent of body weight ≤ 6 months of diagnosis)
- CBC with differential, BUN, creatinine, AST, ALT, albumin, bilirubin, alkaline phosphatase, serum calcium, phosphorus, magnesium, LDH, uric acid
- HIV-1 and HIV-2
- Chest X-ray, PA and lateral
- CT with contrast of neck, chest, abdomen and pelvis
- PET/ CT scan
- Bilateral bone marrow biopsy with aspirate
- Echo or MUGA
- CD4 count
- HIV viral load
- Lumbar puncture with cytology evaluation
- Screening for hepatitis B and C (HBcAb, HBsAg, HCV Ab)
- Consultation to Infectious Diseases
  - Antiretrovirals often can be administered safely with chemotherapy
- Lifestyle risk assessment[1]

OF USE IN SELECTED CASES:

- Upper GI/barium enema/endoscopy
- MRI of brain with gadolinium or CT of brain
- Pregnancy test in women of childbearing potential
- Discussion of fertility issues and sperm banking

See Page 2 for Clinical Presentations and Primary Treatment

[1] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

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AIDS-Related B-Cell Lymphomas

Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION

PRIMARY TREATMENT[1]

Burkitt Lymphoma[2]

- Clinical trial
- Rituximab and dose adjusted EPOCH[3] with intrathecal chemotherapy and filgrastim product
- Rituximab and HCVAD[4] alternating with rituximab and methotrexate and cytarabine with intrathecal chemotherapy and filgrastim product
- Rituximab and CODOX-M[5] alternating with rituximab and IVAC[6] with intrathecal chemotherapy and filgrastim product
- If CD4 < 50 cell/mcL, benefit of rituximab is less clear due to increased infectious complications
- Consider low-intensity therapy with CODOX-M[5]

Double-Hit or Triple-Hit Lymphoma[2]

- Clinical trial
- Regimens as above for Burkitt lymphoma
- Consideration of consolidation in 1st complete remission with high dose chemotherapy and autologous stem cell transplantation (ASCT) in selected patients

See Page 4 for Supportive Care and Page 5 for Response Evaluation

Additional Clinical Presentations and Primary Treatment → See Page 3

[1] Continue anti-retroviral therapy (ART) throughout treatment
[2] CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone is not adequate therapy
[3] EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
[4] HCVAD: cyclophosphamide, vincristine, doxorubicin, and dexamethasone
[5] CODOX-M: cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate
[6] IVAC: ifosfamide, etoposide, and high-dose cytarabine

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AIDS-Related B-Cell Lymphomas

Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION	PRIMARY TREATMENT[1]
Lymphomas associated with Castleman's Disease, Diffuse Large B-cell Lymphoma (DLBCL), or Primary Effusion Lymphomas	• Clinical trial • Rituximab and dose adjusted EPOCH[2] • Rituximab and HCVAD[3] alternating with rituximab, methotrexate and cytarabine • R-CHOP[4] • Filgrastim product in all patients • Intrathecal chemotherapy • If CD4 < 50 cell/microliter, benefit of rituximab is less clear due to increased infectious complications • If CD20 negative, rituximab is not indicated
Plasmablastic Lymphoma[5]	• Clinical trial • HCVAD[3] alternating with methotrexate and cytarabine • Dose adjusted EPOCH[2] • CODOX-M[6] alternating with IVAC[7] • Consider involved field radiation therapy with 36-40 Gy for early stage, localized disease
Primary Central Nervous System (CNS) Diffuse Large B-cell Lymphoma (DLBCL)	• Clinical trial • If good performance status on ART, treat per CNS Diffuse Large B-Cell Lymphoma guideline including initiation of DeAngelis protocol and if in complete remission consider low dose whole brain radiation therapy (WBRT) with 23.4 Gy or consider an ASCT • Rituximab plus high-dose methotrexate • Palliative WBRT • If CD4 < 50 cell/microliter, benefit of rituximab is less clear due to increased infectious complications

See Page 4 for Supportive Care and Page 5 for Response Evaluation

[1] Continue anti-retroviral therapy (ART) throughout treatment
[2] EPOCH: etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin
[3] HCVAD: cyclophosphamide, mesna, doxorubicin, and vincristine
[4] R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
[5] CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone is not adequate therapy
[6] CODOX-M: cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate and leucovorin
[7] IVAC: ifosfamide, etoposide, and cytarabine

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AIDS-Related B-Cell Lymphomas

Note: Consider Clinical Trials as treatment options for eligible patients.

SUPPORTIVE CARE

All diagnoses →

Increased risk of infectious complications mitigated with improved HIV control and aggressive infection prophylaxis:

- Patients not on ART at diagnosis may initiate ART during staging period, or alternately initiate after first cycle of chemotherapy. All ART initiation or changes should be done in consultation with an HIV specialist.
- Zidovudine (AZT), cobicistat, 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 for each cycle
- Pneumocystis jiroveci pneumonia (PJP): continue until CD4 recovery ≥ 200 cell/microliter for ≥ 3 months after completion of chemotherapy
- Gram-negative rods: quinolone prophylaxis or equivalent during period of neutropenia
- Fungal: azole antifungals should be held 24 hours prior to and through 24 hours post chemotherapy with CYP3A4 metabolism
- Mycobacterium avium complex (MAC) prophylaxis for CD4 < 100 cell/microliter
- Strongly consider varicella zoster virus (VZV)/herpes simplex virus (HSV) prophylaxis

Optional:

- Strongly encourage consult with Infectious Diseases for febrile neutropenia in context of extensive prophylaxis as well as for refractory diarrhea

AIDS-Related B-Cell Lymphomas

Note: Consider Clinical Trials as treatment options for eligible patients.

RESPONSE EVALUATION

Complete response (CR) →

Recommend to continue:
- Routine follow-up and management with Infectious Diseases
- Routine cancer screening tests with Primary Cancer physician
- For primary CNS lymphoma, consider consolidative WBRT with 23.4 Gy
- For limited stage DLBCL, consider consolidative radiation with 30.6 Gy in 1.8 Gy fractions

Follow-up:
- Year 1: every 3-4 months
  - Physical exam and labs
  - Repeat CT with contrast
- Years 2-5: every 6 months
  - Physical exam and labs
  - Repeat CT with contrast
- Year 5 and beyond: every 12 months
  - Physical exam and labs

Partial response (PR), stable disease, progressive disease and recurrence →

- Clinical trial
- Consider non-overlapping chemotherapy option per DLBCL guidelines
- Consider high dose chemotherapy plus ASCT for patients who enter into second remission with good performance status and well controlled concomitant medical issues
- Patients with CNS lymphoma who have already received high-dose methotrexate can be considered for WBRT (23.4-30 Gy with or without boost to gross disease) or temozolomide

SUGGESTED READINGS

Aukema, S. M., Siebert, R., Schuuring, E., van Imhoff, G. W., Kluin-Nelemans, H. C., Boerma, E., & Kluin, P. M. (2011). Double-hit B-cell lymphomas. *Blood, 117*(8), 2319-2331. doi:10.1182/blood-2010-09-297879

Barnes, J. A., LaCasce, A. S., Feng, Y., Toomey, C. E., Neuberg, D., Michaelson, J. S., . . . Abramson, J. S. (2011). Evaluation of the addition of rituximab to CODOX-M/IVAC for burkitt's lymphoma: A retrospective analysis. *Annals of Oncology, 22*(8), 1859-1864. doi:10.1093/annonc/mdq677

Barta, S. K., Lee, J. Y., Kaplan, L. D., Noy, A., & Sparano, J. A. (2012). Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. *Cancer, 118*(16), 3977-3983. doi:10.1002/cncr.26723

Barta, S., Xue, X., Wang, D., Tamari, R., Lee, J., Mounier, N., . . . Sparano, J. (2013). A pooled analysis of 1,546 patients with HIV-associated lymphoma: Assessment of lymphoma-, HIV and treatment-specific factors on clinical outcomes. *Blood, 122*(19), 3251-3262. doi:10.1182/blood-2013-04-498964

Bayraktar, U. D., Ramos, J. C., Petrich, A., Gupta, N., Lensing, S., Moore, P. C., . . . Noy, A. (2012). Outcome of patients with relapsed/refractory acquired immune deficiency syndrome-related lymphoma diagnosed 1999-2008 and treated with curative intent in the AIDS malignancy consortium. *Leukemia & Lymphoma, 53*(12), 2383-2389. doi:10.3109/10428194.2012.697559

Blum, K. A., Lozanski, G., & Byrd, J. C. (2004). Adult burkitt leukemia and lymphoma. *Blood, 104*(10), 3009-3020. doi:10.1182/blood-2004-02-0405

Boué, F., Gabarre, J., Gisselbrecht, C., Reynes, J., Cheret, A., Bonnet, F., . . . Costagliola, D. (2006). Phase II trial of CHOP plus rituximab in patients with HIV-associated non-hodgkin's lymphoma. *Journal of Clinical Oncology, 24*(25), 4123-4128. doi:10.1200/JCO.2005.05.4684

Cheson, B., Pfistner, B., Juweid, M., Gascoyne, R., Specht, L., Horning, S., . . . Diehl, V. (2007). Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology, 25*(5), 579-586. doi:10.1200/JCO.2006.09.2403

Cortes, J., Thomas, D., Rios, A., Koller, C., O'Brien, S., Jeha, S., . . . Kantarjian, H. (2002). Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related burkitt lymphoma/leukemia. *Cancer, 94*(5), 1492-1499. doi:10.1002/cncr.10365

Dunleavy, K., Little, R., Pittaluga, S., Grant, N., Shovlin, M., Steinberg, S., . . . Wilson, W. (2008). A prospective study of dose-adjusted (DA) epoch with rituximab in adults with newly diagnosed burkitt lymphoma: A regimen with high efficacy and low toxicity. *Annals of Oncology, 19*, 83-84. Retrieved from https://academic.oup.com/annonc

Dunleavy, K., Little, R. F., Pittaluga, S., Grant, N., Wayne, A. S., Carrasquillo, J. A., . . . Wilson, W. H. (2010). The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma. *Blood, 115*(15), 3017-3024. doi:10.1182/blood-2009-11-253039

Dunleavy, K., Pittaluga, S., Shovlin, M., Steinberg, S., Cole, D., Grant, C., . . . Wilson, W. (2013). Low-intensity therapy in adults with burkitt's lymphoma. *New England Journal of Medicine, 369*(20), 1915-1925. doi:10.1056/NEJMoa1308392

Continued on next page

SUGGESTED READINGS - continued

Kaplan, L. D., Lee, J. Y., Ambinder, R. F., Sparano, J. A., Cesarman, E., Chadburn, A., . . . Scadden, D. T. (2005). Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-hodgkin lymphoma: AIDS-malignancies consortium trial 010. *Blood, 106*(5), 1538-1543. doi:10.1182/blood-2005-04-1437

Levine, A. M., Seneviratne, L., Espina, B. M., Wohl, A. R., Tulpule, A., Nathwani, B. N., & Gill, P. S. (2000). Evolving characteristics of AIDS-related lymphoma. *Blood, 96*(13), 4084-4090. Retrieved from http://search.proquest.com/docview/72468157

Lim, S. T., Karim, R., Nathwani, B. N., Tulpule, A., Espina, B., & Levine, A. M. (2005). AIDS-related burkitt's lymphoma versus diffuse large-cell lymphoma in the Pre–Highly active antiretroviral therapy (HAART) and HAART eras: Significant differences in survival with standard chemotherapy. *Journal of Clinical Oncology, 23*(19), 4430-4438. doi:10.1200/JCO.2005.11.973

Little, R. F., Pittaluga, P., Grant, N., Steinberg, S. M., Kavlick,M. F., Mitsuya, H., Franchini, G., . . . Wilson, W. H. (2003). Highly effective treatment of acquired immuno- deficiency syndrome-related lymphoma with dose-adjusted EPOCH: Impact of antiretroviral therapy suspension and tumor biology. *Blood, 101*(12), 4653-4659. doi.org/10.1182/blood-2002-11-3589

Newell, M. E., Hoy, J. F., Cooper, S. G., DeGraaff, B., Grulich, A. E., Bryant, M., . . . Quinn, D. I. (2004). Human immunodeficiency virus–related primary central nervous system lymphoma. *Cancer*, 100(12), 2627-2636. doi:10.1002/cncr.20300

Magrath, I., Adde, M., Shad, A., Venzon, D., Seibel, N., Gootenberg, J., . . . Horak, I. D. (1996). Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. *Journal of Clinical Oncology, 14*(3), 925-934. doi:10.1200/JCO.1996.14.3.925

Mead, G., Sydes, M., Walewski, J., Grigg, A., Hatton, C., Norbert, P., . . . Wright, D. (2002). An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult burkitt's lymphoma: Results of united kingdom lymphoma group LY06 study. *Annals of Oncology, 13*(8), 1264-1274. doi:10.1093/annonc/mdf253

Morris, P. G., Correa, D. D., Yahalom, J., Raizer, J. J., Schiff, D., Grant, B., . . . Omuro, A. (2013). Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: Final results and long-term outcome. *Journal of Clinical Oncology, 31*(31), 3971-3971. doi:10.1200/JCO.2013.50.4910

Mounier, N., Spina, M., & Gisselbrecht, C. (2007). Modern management of non-hodgkin lymphoma in HIV-infected patients. *British Journal of Haematology, 136*(5), 685-698. doi:10.1111/j.1365-2141.2006.06464.x

National Comprehensive Cancer Network. (2019). *B-cell lymphomas.* (NCCN Guideline Version 4.2019). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

Noy, A., Kaplan L., & Lee, J. Y. (2013). A modified dose intensive R- CODOX-M/IVAC for HIV-associated Burkitt and atypical burkitt lymphoma (BL) demonstrates high cure rates and low toxicity: Prospective multicenter phase II trial of The AIDS Malignancy Consortium (ACM 048). *Blood*, *122*, 639. Retrieved from https://ashpublications.org/blood/issue/122/21

Continued on next page

SUGGESTED READINGS - continued

Oki, Y., Noorani, M., Davis, R., Neelapu, S., Rodriguez, A., Hagemeister, F., . . . Fayad, L. (2013). Double hit lymphoma: MD Anderson experience. *Blood*, *122*(21), 1776. Retrieved from https://ashpublications.org/blood/issue/122/21

Ribera, J., Oriol, A., Morgades, M., Gonzalez-Barca, E., Miralles, P., Lopez-Guillermo, A., . . . García, M. (2008). Safety and efficacy of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab in patients with human immunodeficiency virus-associated diffuse large B-cell lymphoma: Results of a phase II trial. *British Journal of Haematology*, *140*(4), 411-419. doi:10.1111/j.1365-2141.2007.06943.x

Sparano, J. A., Lee, J. Y., Kaplan, L. D., Levine, A. M., Ramos, J. C., Ambinder, R. F., . . . Mitsuyasu, R. (2010). Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-hodgkin lymphoma. *Blood*, *115*(15), 3008-3016. doi:10.1182/blood-2009-08-231613

Thomas, D. A., Faderl, S., O'Brien, S., Bueso-Ramos, C., Cortes, J., Garcia-Manero, G., . . . Kantarjian, H. (2006). Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult burkitt and burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer*, *106*(7), 1569-1580. doi:10.1002/cncr.21776

Thomas, D., Kantarjian, H., Cortes, J., Faderl, S., Wierda, W., Ravandi, F., . . . O'Brien, S. (2008). Long-term outcome after hyper-CVAD and rituximab chemoimmunotherapy for burkitt (BL) or burkitt-like (BLL) leukemia/lymphoma and mature B-cell acute lymphocytic leukemia (ALL). *Blood*, *112*(11), 673-674. Retrieved from https://ashpublications.org/blood/issue/122/21

Wang, E. S., Straus, D. J., Teruya-Feldstein, J., Qin, J., Portlock, C., Moskowitz, C., . . . Noy, A. (2003). Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus–associated burkitt lymphoma. *Cancer*, *98*(6), 1196-1205. doi:10.1002/cncr.11628

Weiss, R., Mitrou, P., Arasteh, K., Schuermann, D., Hentrich, M., Duehrsen, U., . . . Huhn, D. (2006). Acquired immunodeficiency syndrome-related lymphoma. *Cancer*, *106*(7), 1560-1568. doi:10.1002/cncr.21759

DEVELOPMENT CREDITS

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