National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin's Lymphomas

Version 2.2015

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Diffuse Large B-Cell Lymphoma

DIAGNOSIS[a,b]

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 and GCB versus non-GCB origin[c,d]**
  - **IHC panel: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1, MYC**
    or
  - **Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, CD20**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **Additional immunohistochemical studies to establish lymphoma subtype**
  - **IHC panel: Cyclin D1, kappa/lambda, CD30, CD138, EBER-ISH, ALK, HHV8**
- **Cytogenetics or FISH: t(14;18),[e] t(3;v), t(8;14), t(8;v)**

SUBTYPES

- **Subtypes included:**
  - **DLBCL, NOS[f]**
  - **DLBCL coexistent with follicular lymphoma of any grade**
  - **DLBCL coexistent with gastric MALT lymphoma**
  - **DLBCL coexistent with nongastric MALT lymphoma**
  - **Follicular lymphoma grade 3[g]**
  - **Intravascular large B-cell lymphoma**
  - **DLBCL associated with chronic inflammation**
  - **ALK-positive DLBCL**
  - **EBV-positive DLBCL of the elderly**
  - **T-cell-/histiocyte-rich large B-cell lymphoma**

→ **See Workup (BCEL-2)**

- **Subtypes *not* included:**
  - **Primary cutaneous B-cell lymphomas (See CUTB-1)**
  - **Primary DLBCL of the CNS (See NCCN Guidelines for CNS)**

Primary Mediastinal Large B-Cell Lymphoma (PMBL), see BCEL-B 1 of 2.
Grey Zone Lymphoma, see BCEL-B 2 of 2.

[a] Burkitt lymphoma intermediate histology or DLBCL CD10+ tumors with very high proliferation >90% with or without Burkitt lymphoma-like features might be considered for more aggressive treatment as per BURK-A. These cases would be appropriate to evaluate for *BCL2*, *BCL6,* and *MYC* rearrangements.

[b] See International Prognostic Index (BCEL-A).

[c] Typical immunophenotype: CD20+, CD45+, CD3-; other markers used for subclassification.

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

[e] There are no established guidelines to select DLBCL patients to investigate for double-hit lymphomas. Standard of care is not established for DLBCL with t(14;18) with concurrent MYC rearrangements.

[f] Germinal center (or follicle center) phenotype is not equivalent to follicular lymphoma and can occur in DLBCL and Burkitt lymphoma. Morphology is required to establish diagnosis.

[g] Controversy exists regarding management of FL grade 3. Some may treat FL grade 3a as follicular lymphoma and others may treat it as DLBCL.

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
- Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET-CT scan
- Adequate bone marrow biopsy (>1.6 cm) ± aspirate; bone marrow may not be needed if PET scan negative unless finding of another lymphoma subtype is important for treatment decision
- Calculation of International Prognostic Index (IPI)[b]
- Hepatitis B testing[h]
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age

USEFUL IN SELECTED CASES:

- Neck CT, head CT, or MRI
- Discussion of fertility issues and sperm banking
- HIV
- Lumbar puncture, consider if paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or ≥2 extranodal sites and elevated LDH
- Beta-2-microglobulin

→ See Induction Therapy (BCEL-3)

[b] See International Prognostic Index (BCEL-A).

[h] 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.

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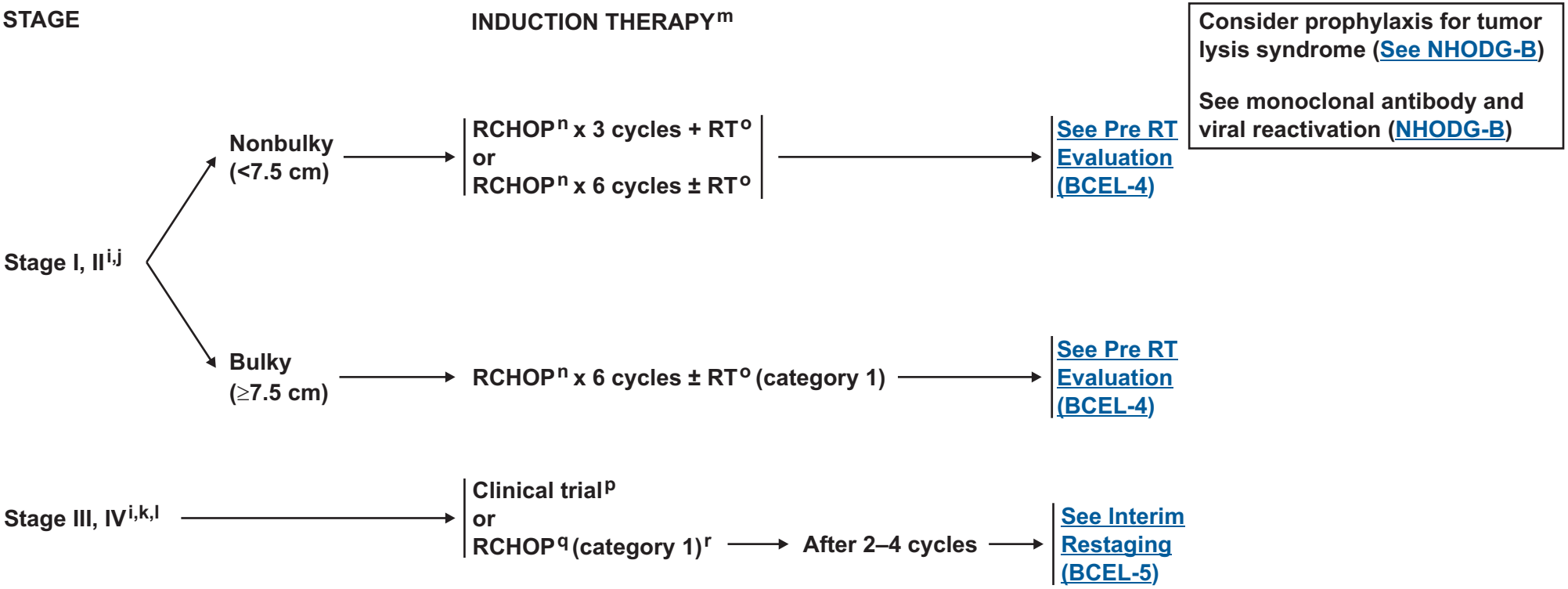

[i] In testicular lymphoma, after completion of chemotherapy, scrotal RT should be given (25–30 Gy).

[j] In patients who are not candidates for chemotherapy, involved-site radiation therapy (ISRT) is recommended.

[k] In selected cases (paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, kidney or adrenal gland involvement, concurrent expression of MYC and BCL2 protein, or ≥2 extranodal sites and elevated LDH), there may be an increased risk of CNS events. The optimal management of these events is uncertain, but CNS prophylaxis can be considered with 4–8 doses of intrathecal methotrexate and/or cytarabine, or systemic methotrexate (3–3.5 g/m^2) during the course of treatment. Recent data regarding stage IE DLBCL of the breast have been suggested as a potential risk for CNS disease. See Prognostic Model for Assessing Risk of CNS Disease (BCEL-A 2 of 2).

[l] For systemic disease with concurrent CNS disease, see BCEL-C.

[m] Recommendations are for HIV-negative lymphoma only. For HIV-positive DLBCL, see AIDS-2.

[n] For patients who cannot tolerate anthracyclines, see BCEL-C for regimens for patients with poor left ventricular function.

[o] See Principles of Radiation Therapy (NHODG-D).

[p] May include high-dose therapy.

[q] Based on current clinical trials, CHOP is preferable due to reduced toxicities, but other comparable anthracycline-based regimens are acceptable (see BCEL-C).

[r] In selected cases, RT to initially bulky sites of disease may be beneficial (category 2B).

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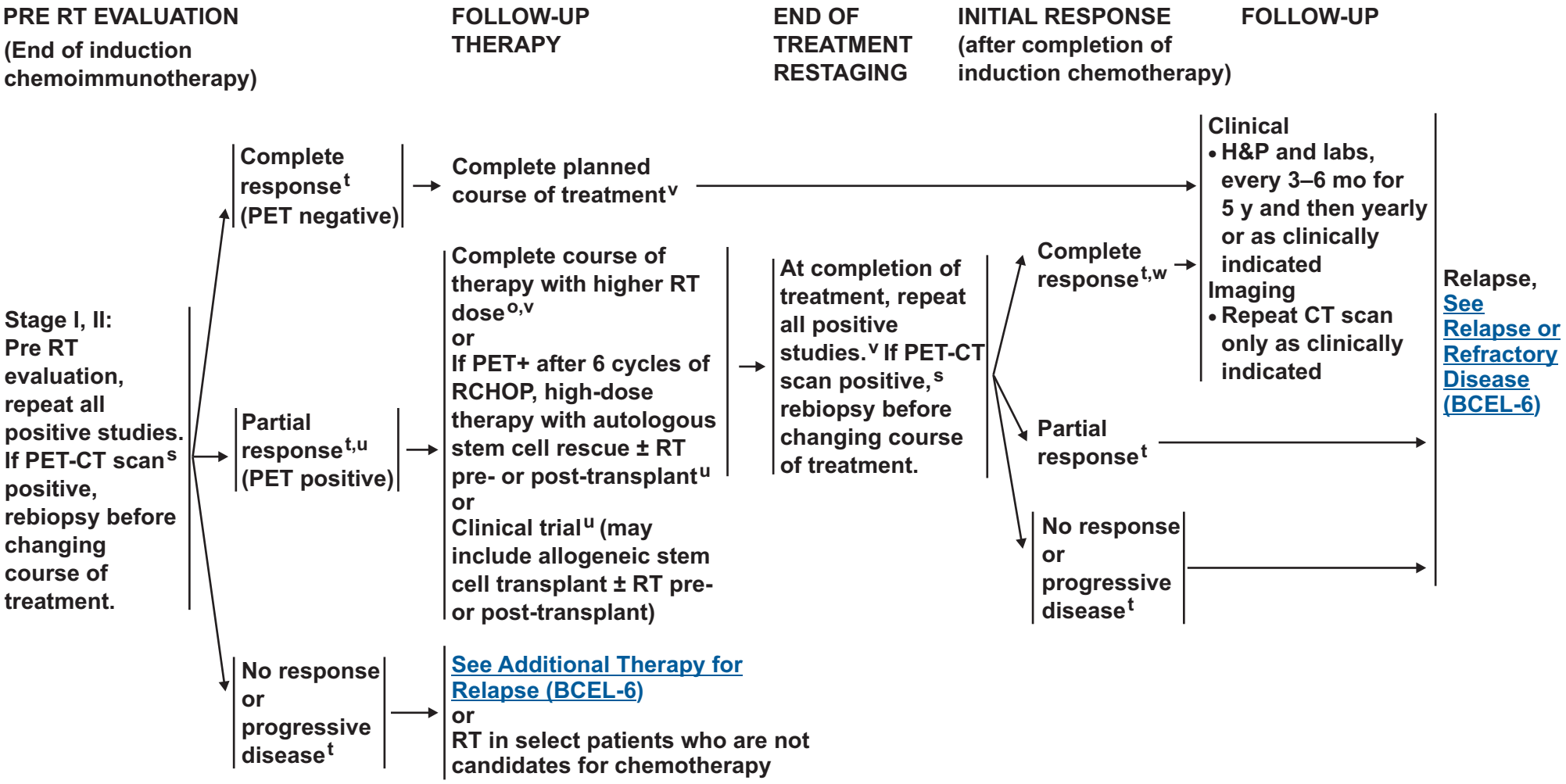

[o] See Principles of Radiation Therapy (NHODG-D).

[s] PET-CT scan should be interpreted via the PET Five Point Scale (See NHODG-C 3 of 3).

[t] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[u] Repeat biopsy should be strongly considered in PET positive prior to additional therapy.

[v] The optimum timing of repeat PET-CT is unknown; however, waiting a minimum of 8 weeks after RT to repeat PET-CT scan is suggested. False positives may occur due to posttreatment changes.

[w] Patients in first remission may be candidates for consolidation trials including high-dose therapy with autologous stem cell rescue.

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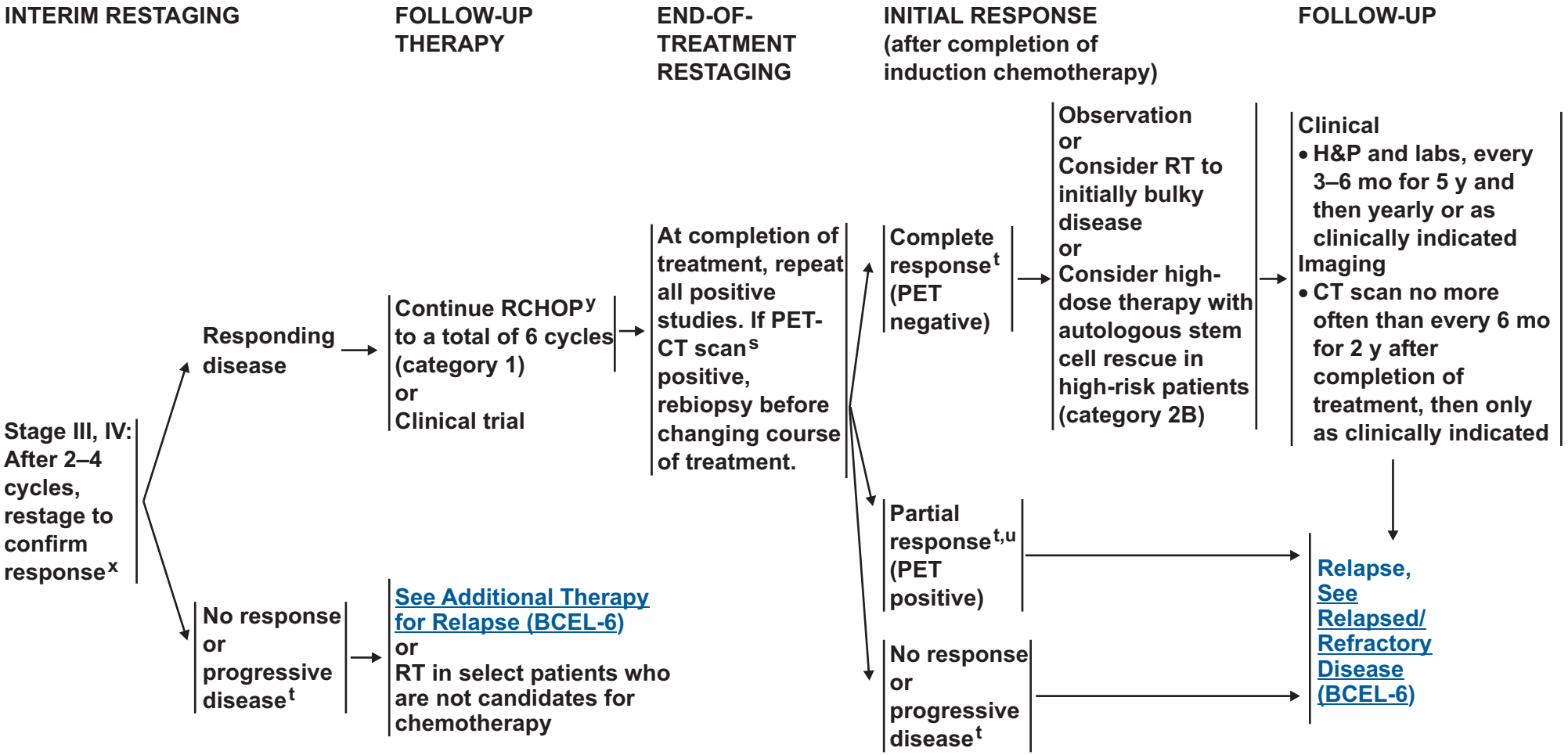

[s] PET-CT scan should be interpreted via the PET Five Point Scale (See NHODG-C 3 of 3).

[t] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[u] Repeat biopsy should be strongly considered in PET positive prior to additional therapy.

[x] PET-CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET-CT scan performed and positive, rebiopsy before changing course of treatment.

[y] For other regimens, see BCEL-C.

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RELAPSE/ REFRACTORY DISEASE | **ADDITIONAL THERAPY** | **RESPONSE #2** | **CONSOLIDATION/ ADDITIONAL THERAPY** | **RELAPSE #2 OR GREATER**

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

See monoclonal antibody and viral reactivation (NHODG-B)

Relapse/ refractory disease[l]

For patients with intention to proceed to high-dose therapy

Second-line therapy See Suggested Regimens (BCEL-C)

Complete response[t] **or Partial response**[t]

High-dose therapy with autologous stem cell rescue (category 1 for CR, category 2A for all others) ± IFRT[z] **or Clinical trial or Allogeneic stem cell transplant in selected cases**[aa]

No response

Non-candidates for high-dose therapy

Clinical trial or Second-line therapy See Suggested Regimens (BCEL-C) or Palliative RT or Best supportive care

Clinical trial[bb] **or Alternative second-line therapy (See BCEL-C) or Palliative RT or Best supportive care**

[l] For systemic disease with concurrent CNS disease, see BCEL-C.

[t] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[z] Additional RT can be given before or after high-dose therapy with stem cell rescue to sites of previous positive disease.

[aa] Selected cases include mobilization failures and persistent bone marrow involvement.

[bb] Clinical trials or individual regimens: Patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with a long disease-free interval.

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INTERNATIONAL PROGNOSTIC INDEX[a]

ALL PATIENTS:
- Age >60 years
- Serum LDH > normal
- Performance status 2–4
- Stage III or IV
- Extranodal involvement >1 site

INTERNATIONAL INDEX, ALL PATIENTS:

• Low	0 or 1
• Low intermediate	2
• High intermediate	3
• High	4 or 5

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:
- Stage III or IV
- Serum LDH > normal
- Performance status 2–4

INTERNATIONAL INDEX, PATIENTS ≤60 YEARS:

• Low	0
• Low/intermediate	1
• High/intermediate	2
• High	3

NCCN-IPI[b]

Age, years	
>40 to ≤60	1
>60 to <75	2
≥75	3
LDH, normalized	
>1 to ≤3	1
>3	2
Ann Arbor stage III-IV	1
Extranodal disease*	1
Performance status ≥2	1

Risk group

• Low	0–1
• Low-intermediate	2–3
• High-intermediate	4–5
• High	≥6

*Disease in bone marrow, CNS, liver/GI tract, or lung.

[a] The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med1993; 329:987-994.

[b] This research was originally published in *Blood*. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014;123:837-842. © the American Society of Hematology

Back to Workup (BCEL-2)

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.

Prognostic Model to Assess the Risk of CNS Disease[1,2]

- Age >60 years
- Serum LDH > normal
- Performance status >1
- Stage III or IV
- Extranodal involvement >1 site
- Kidney or adrenal gland involvement

Low risk	0-1
Intermediate-risk	2-3
High-risk	4-6

[1] Schmitz N, Zeynalova S, Nickelsen M, et al. A new prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma [abstract]. Hematol Oncol 2013;31 (Suppl. 1):96-150; Abstract 047.

[2] Savage K, et al Validation of a prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma [abstract]. Blood 2014;124(21):Abstract 394.

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.

Primary Mediastinal Large B-Cell Lymphoma

Primary mediastinal large B-cell lymphoma (PMBL) can be defined as a clinical entity presenting with primary site of disease in mediastinum with or without other sites and has histology of DLBCL. PBML overlaps with grey zone lymphomas that have intermediate features between Hodgkin lymphoma and PMBL and have unique diagnostic characteristics.
See Grey Zone Lymphoma (BCEL-B 2 of 2).

- **Clinical pathologic correlation is required to establish diagnosis.**

- **Optimal first-line therapy is more controversial than other subtypes of NHL; however, treatment regimens include:**
  - **RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) x 6 cycles + RT**
  - **Dose-adjusted EPOCH-R ([etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab)[a] x 6 cycles; for persistent focal disease, RT can be added.**
  - **RCHOP x 4 cycles followed by ICE (ifosfamide, carboplatin, etoposide)[b] x 3 cycles ± RT (category 2B)**

- **Role of RT is controversial. If PET-CT scan was negative at the end of treatment and initial disease was non-bulky, observation may be considered.**

- **Residual mediastinal masses are common. PET-CT scan is essential post-treatment. Biopsy of PET-CT scan positive mass is recommended if additional systemic treatment is contemplated.**

[a] Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013;368:1408-1416.
[b] Moskowitz C, Hamlin PA, Jr., Maragulia J, et al. Sequential dose-dense RCHOP followed by ICE consolidation (MSKCC protocol 01-142) without radiotherapy for patients with primary mediastinal large B-cell lymphoma [abstract]. Blood 2010;116:Abstract 420.

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Grey Zone Lymphoma

Synonyms
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (CHL)
- Large B-cell lymphoma with Hodgkin features
- Hodgkin-like anaplastic large cell lymphoma

Clinical Presentation
- Present with large anterior mediastinal mass with or without supraclavicular lymph nodes
  - More common in males, presenting between 20–40 y

Morphology
- Pleomorphic cells in a diffusely fibrous stroma
- Typically larger and more pleomorphic than in PMBL, sometimes resembling lacunar or Hodgkin-like cells
- Necrosis without neutrophilic infiltrate is frequent

Immunophenotype
- Often transitional features between CHL and PMBL
- CD45 often positive; CD30, CD15, CD20, CD79a frequently positive
- EBV - (<20% of cases +)
- PAX5, BOB.1, OCT-2 are often positive, BCL6 variable
- CD10, ALK are negative
- If morphology closer to PMBL, absence of CD20, CD15+ or the presence of EBV would suggest the diagnosis of grey zone lymphoma
- If morphology closer to CHL, CD20 strong positivity and other B-cell markers and absence of CD15-would suggest grey zone lymphoma.

Prognosis and Treatment
- A worse prognosis than either CHL or PMBL has been suggested.
- While there is no consensus on the treatment, aggressive large B-cell lymphoma [or Hodgkin type] regimens have been proposed.
- If the tumor cells are CD20+, the addition of rituximab to the chemotherapy treatment should be considered.
- Data suggest that the use of rituximab-anthracycline-based chemotherapy as in other B-cell lymphomas (See BCEL-C) is helpful. If localized disease, then ± RT.

References:

Dunleavy K, Pittaluga S, Tay K, et al. Comparative clinical and biological features of primary mediastinal B-cell lymphoma (PMBL) and mediastinal grey zone lymphoma (MGZL) [abstract]. Blood 2009;114:Abstract 106.

Jaffe ES, Stein H, Swerdlow SH, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:267-268.

Quintanilla-Martinez L, de Jong D, de Mascarel A, et al. Gray zones around diffuse large B cell lymphoma. Conclusions based on the workshop of the XIV meeting of the European Association for Hematopathology and the Society of Hematopathology in Bordeaux, France. J Hematop 2009;2:211-236.

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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

First-line Therapy

- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- Dose-dense RCHOP 14 (category 3)
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (category 2B)

First-line Therapy for Patients with Poor Left Ventricular Function or Very Frail[b,c]

- RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
- RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
- RCNOP (rituximab, cyclophosphamide, mitoxantrone, vincristine, prednisone)
- DA-EPOCH[d] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
- RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)

Patients >80 Years of Age with Comorbidities

- R-mini-CHOP

First-line Consolidation (optional)

- Age-adjusted IPI high-risk disease: High-dose therapy with autologous stem cell rescue (category 2B)
- Double-hit DLBCL: High-dose therapy with autologous stem cell rescue

See Second-line Therapy on BCEL-C 2 of 4.

Concurrent Presentation with CNS Disease

- Parenchymal: 3 g/m^2 or more of systemic methotrexate given on Day 15 of a 21-day RCHOP cycle that has been supported by growth factors.
- Leptomeningeal: IT methotrexate/cytarabine, consider Ommaya reservoir placement and/or systemic methotrexate (3–3.5 g/m^2)

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

See monoclonal antibody and viral reactivation (NHODG-B)

[a] See references for regimens BCEL-C 3 of 4 and BCEL-C 4 of 4.
[b] Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[c] There are limited published data regarding the use of these regimens; however, they are used at NCCN Member Institutions for the first-line treatment of DLBCL for patients with poor left ventricular function.
[d] If upward dose adjustment is necessary, doxorubicin should be maintained at base dose and not increased.

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SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

Second-line and Subsequent Therapy[b,e,f] (intention to proceed to high-dose therapy)

- DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx (gemcitabine, oxaliplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

Second-line and Subsequent Therapy[b,e,f] (non-candidates for high-dose therapy)

- Bendamustine ± rituximab
- Brentuximab vedotin for CD30+ disease (category 2B)
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab - PO and IV
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DA-EPOCH ± rituximab
- GDP ± rituximab
- GemOx ± rituximab
- Lenalidomide ± rituximab
- Rituximab

See First-line Therapy on BCEL-C 1 of 4.

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

See monoclonal antibody and viral reactivation (NHODG-B)

[a] See references for regimens BCEL-C 3 of 4 and BCEL-C 4 of 4.
[b] Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[e] If additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.
[f] Rituximab should be included in second-line therapy if there is relapse after a reasonable remission (>6 mo); however; rituximab should often be omitted in patients with primary refractory disease.

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SUGGESTED TREATMENT REGIMENS
References

First-line Therapy

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab with RT

Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-hodgkin's lymphoma. N Engl J Med 1998;339:21-26.

Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-hodgkin's lymphoma: Eastern Cooperative Oncology Group Study 1484. J Clin Oncol 2004;22:3032-3038.

Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group Study 0014. J Clin Oncol 2008;26:2258-2263.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab

Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-2045.

Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117-4126.

Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379-391.

Dose-dense CHOP 14 + rituximab

Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105-116.

Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 2013;381:1817-1826.

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

Purroy N, Lopez A, Vallespi T, Gironella M, Bergua J, Sancho JM. Dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor risk large B-cell lymphoma. A phase 2 study conducted by the Spanish PETHEMA Group [Abstract]. Blood 2009;114:Abstract 2701.

Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. J Clin Oncol 2008;26:2717-2724.

Wilson WH, Jung SH, Porcu P, et al. A Cancer and Leukemia Group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype. Haematologica 2012;97:758-765.

First-line Therapy for Patients with Poor Left Ventricular Function

CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) + rituximab

Martino R, Perea G, Caballero MD, et al. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: Results from a prospective phase II study. Haematologica 2002;87:822-827.

Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2006;47:2174-2180.

CNOP (cyclophosphamide, mitoxantrone, vincristine, prednisone) + rituximab

Bessell EM, Burton A, Haynes AP, et al. A randomised multicentre trial of modified CHOP versus MCOP in patients aged 65 years and over with aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14:258-267.

Bezwoda W, Rastogi RB, Erazo Valla A, et al. Long-term results of a multicentre randomised, comparative phase III trial of CHOP versus CNOP regimens in patients with intermediate- and high-grade non-Hodgkin's lymphomas. Novantrone International Study Group. Eur J Cancer 1995;31A:903-911.

Sonneveld P, de Ridder M, van der Lelie H, et al. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. J Clin Oncol 1995;13:2530-2539.

RCEOP (ritximab, cyclophosphamide, etoposide, vincristine, prednisone)

Moccia A, Schaff K, Hoskins P, et al. R-CHOP with etoposide substituted for doxorubicin (R-CEOP): Excellent outcome in diffuse large B cell lymphoma for patients with a contraindication to anthracyclines [abstract]. Blood 2009;114:Abstract 408.

First-line therapy for elderly patients (age >80 years)

R-mini-CHOP

Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol 2011;12:460-468.

First-line Consolidation

Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. N Engl J Med 2013;369:1681-1690.

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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.

SUGGESTED TREATMENT REGIMENS
References

Second-line and Subsequent Therapy

Bendamustine ± rituximab

Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;13:1285-1289.

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Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2013;31:2103-2109.

Brentuximab vedotin

Bartlett, N, Sharman J, Oki Y, et al. A phase 2 study of brentuximab vedotin in patients with relapsed or refractory CD30-positive non-Hodgkin lymphomas: Interim results in patients with DLBCL and other B-Cell lymphomas [abstract]. Blood 2013;122; Abstract:848.

DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab

Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988;71:117-122.

Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer Invest 2006;24:593-600.

Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-4190.

ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab

Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP - an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 1994;12:1169-1176.

Martin A, Conde E, Arnan M, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica 2008;93:1829-1836.

GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab

Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer 2004;101:1835-1842.

GDP (gemcitabine, dexamethasone, carboplatin) ± rituximab

Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by the Puget Sound Oncology Consortium. Leuk Lymphoma 2010;51:1523-1529.

GemOX (gemcitabine, oxaliplatin) + rituximab

Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study. Eur J Haematol 2008;80:127-132.

ICE (ifosfamide, carboplatin, etoposide) ± rituximab

Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2003;14[suppl 1]:i5-10.

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Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-4190.

Lenalidomide ± rituximab

Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol 2011;22:1622-1627.

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Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular, and transformed lymphoma: a phase II clinical trial. Leukemia 2013;27:1902-1909.

CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab

Chao NJ, Rosenberg SA, and Horning SJ. CEPP(B): An effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. Blood 1990;76:1293-1298.

EPOCH + rituximab

Gutierrez M, Chabner BA, Pearson D, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: An 8-year follow-up study of EPOCH. J Clin Oncol 2000;18:3633-3642.

Jermann M, Jost LM, Taverna C, et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: Results of a phase II study. Ann Oncol 2004;15:511-516.

RGemOx (rituximab, gemcitabine, oxaliplatin)

Corazzelli G, Capobianco G, Arcamone M, et al. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. Cancer Chemother Pharmacol 2009;64:907-916.

El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: An effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. Ann Oncol 2007;18:1363-1368.

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Diffuse Large B-Cell Lymphoma

Diagnosis

Diffuse large B-cell lymphomas (DLBCL) are the most common lymphoid neoplasms in adults, accounting for approximately 30% of NHLs diagnosed annually.[1] DLBCL NOS, FL (grade 3 only), DLBCL coexistent with a low-grade lymphoma of any kind (e.g., FL of any grade, gastric MALT or non-gastric MALT lymphoma), intravascular large B-cell lymphoma, DLBCL associated with chronic inflammation, ALK-positive DLBCL, EBV-positive DLBCL of the elderly and T-cell/histiocyte rich large B-cell lymphoma are also managed according to the DLBCL guidelines.

Gene expression profiling studies have revealed significant heterogeneity within DLBCL.[2] However, incorporation of this information into treatment algorithms awaits further investigation. Immunohistochemical markers such as CD10, BCL6, and IRF4/MUM1 have been reported to recapitulate the gene expression profiling in classifying DLBCL into 2 different subtypes: germinal center B-cell (GCB) subtype (CD10+, or BCL6+, IRF4/MUM1-) and non-GCB subtype (CD10-, IRF4/MUM1+ or BCL6-, IRF4/MUM1-).[3] However, the validity of this classification has been brought into question. An improved immunohistochemical algorithm has been proposed which includes GCET1, FOXP1, BCL6, IFR4/MUM1, and CD10.[4,5] Although GCB subtype is associated with an improved outcome compared to non-GCB subtype, treatment remains the same for both the subtypes and cell-of-origin should not be used to guide the selection of therapy.

MYC rearrangement has been reported in 9% to 17% of patients with DLBCL, and often correlates with GCB phenotype.[6-8] DLBCL with concurrent *BCL2* and *MYC* rearrangements are known as "double-hit" lymphomas that are characterized by highly aggressive clinical behavior and overlapping pathologic features with Burkitt lymphoma (BL), B lymphoblastic lymphoma/leukemia (B-LBL), and DLBCL.[9] "Double-hit" lymphomas have been observed in 2% to 11% of newly diagnosed patients with DLBCL. Patients with "double-hit" lymphomas have very poor clinical outcomes, even with rituximab-containing chemoimmunotherapy or intensive therapy with stem cell transplantation.[6-8,10] Immunohistochemical staining can also identify DLBCL with dual expression of both MYC and BCL2 proteins ("double-expressing" DLBCL).[11,12] These patients have an inferior prognosis compared to those with DLBCL as a whole, but not to the same magnitude as patients with true "double-hit" lymphomas on the basis of genetic rearrangements. No guidelines are available for the treatment of patients with "double-hit" lymphomas with concurrent *MYC* and *BCL2* rearrangements nor for "double-expressing" lymphomas, as the standard of care for these patients have not been established. Additional data on the management of these high-risk disease subtypes is needed.

Adequate immunophenotyping is required to establish the diagnosis and to determine GCB versus non-GCB origin. The typical immunophenotype is CD20+, CD45+, and CD3-. The recommended immunophenotyping panel includes CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1 and MYC. When available, GCET1 and FOXP1 can provide information necessary for the Choi IHC cell of origin algorithm. Additional markers such as CD138, CD30, cyclin D1, ALK1, EBV and HHV-8 may be useful under certain circumstances to establish the subtype. Molecular genetic analysis for detection of gene rearrangements in *CCND1, BCL6*, or *MYC*, as well as conventional or FISH cytogenetic for detection of the translocations, t(14;18), t(3;v), t(8;14) or t(8;v) may also be useful in some cases.

Workup

The initial workup for newly diagnosed patients with DLBCL should include a thorough physical examination with attention to node-bearing areas, and evaluation of performance status and constitutional symptoms. Laboratory assessments should include standard blood work including CBC with differential and a comprehensive metabolic panel, in addition to measurements of serum lactate dehydrogenase (LDH) and serum beta-2-microglobulin levels. Patients with high tumor burden and elevated LDH should be assessed for spontaneous tumor lysis syndrome, including measurements of uric acid level. HBV testing is recommended due to increased risks of viral reactivation when immunotherapy regimens are being considered for treatment. Adequate trephine biopsy (specimen ≥1.6 cm)[13,14] should be obtained for initial staging evaluation, with or without bone marrow aspiration.

The staging workup is designed to identify all sites of known disease and determine prognosis with known clinical risk factors. Risk factors used to determine International Prognostic Index (IPI) scores include age, stage of disease, LDH level, performance status, and the number of extra-nodal sites of disease.[15] In patients who are 60 years or younger, the prognostic factors include tumor stage, performance status, and serum LDH level. The IPI and age-adjusted IPI can be used to identify specific group of patients who are more or less likely to be cured with standard therapy.[15] Zhou et al recently reported an enhanced IPI (NCCN-IPI) to stratify patients with newly diagnosed DLBCL into 4 different risk groups (low, low-intermediate, high-intermediate, and high) based on their clinical features (age, LDH, sites of involvement, Ann Arbor stage, ECOG performance status).[16] This analysis included 1650 patients identified in NCCN database who were diagnosed with DLBCL from 2000-2010 and treated with rituximab-based therapy. The NCCN-IPI discriminated patients in the low- and high-risk subgroups better (5-year OS rate 96% vs 33%) than the IPI (5 year OS rate 90% vs 54%). NCCN-IPI was also validated using an independent cohort of 1138 patients from the British Columbia Cancer Agency.

PET or PET-CT scans, have a more clear-cut role in selected cases of DLBCL than in other lymphoid neoplasms. PET scans are particularly informative in the initial staging where upstaging resulting in altered therapy occurs about 9% of the time, and for response evaluation after treatment because they can distinguish residual fibrotic masses from masses containing viable tumor. As PET scans have now been incorporated into the response criteria, availability of a baseline study is necessary for optimal interpretation of the post-treatment study. In some centers, beta-2-microglobulin is considered a major determinant of risk (category 2B). Lumbar puncture is recommended in patients with one or more of the following sites of involvement: paranasal sinus, testicular, epidural, HIV-associated lymphoma, bone marrow (with large cells) or the presence of 2 or more extranodal sites and elevated LDH levels. Diagnostic yield is improved if flow cytometric analysis of CSF is undertaken. Patients with these risk factors should also be considered for prophylactic chemotherapy for the CNS.

Treatment Options by Clinical Stage

Treatment options for DLBCL differ between patients with localized (Ann Arbor stage I-II) and advanced (Ann Arbor stage III-IV) disease. Prognosis is extremely favorable for patients with no adverse risk factors (elevated LDH, stage II bulky disease, older than 60 years or ECOG performance status of 2 or more). Patients with advanced disease should be enrolled in clinical trials, whenever possible.

Stage I-II

In the SWOG 8736 study, 3 cycles of CHOP followed by involved field radiation therapy (IFRT) produced significantly better progression-free

survival (PFS; 5-year estimated PFS: 77% vs. 64% for CHOP alone) and OS (82% vs. 72% for CHOP alone) than 8 cycles of CHOP alone in patients with localized aggressive NHL;[17] however, this difference disappeared with further follow-up. The benefit of CHOP (3 cycles) followed by IFRT (5-year OS of 95%) in patients with limited-stage DLBCL (60 years or younger with no adverse risk factors) was also confirmed in a series from the British Columbia Cancer Agency.[18] Another randomized trial (ECOG 1484 study) showed that the addition of RT to CHOP (8 cycles) prolonged disease-free survival (DFS) in patients with limited stage DLBCL who had achieved CR to CHOP alone (6-year DFS was 73% for IFRT and 56% for observation).[19] In the GELA study (LNH 93-4), the addition of RT to 4 cycles of CHOP did not provide any advantage over 4 cycles of CHOP alone for the treatment of elderly patients with low-risk localized aggressive lymphoma. The estimated 5-year event-free survival (EFS) was not different between the two groups (61% and 64%, respectively) and the 5-year estimated OS rate was 68% and 72%, respectively.[20] However, in this study, administration of RT was markedly delayed and 12% of patients on the RT arm did not receive RT.

The efficacy of the addition of rituximab to CHOP (R-CHOP) and IFRT has also been reported in patients with limited stage DLBCL. In the SWOG 0014 study that evaluated 3 cycles of R-CHOP followed by IFRT in patients with at least one adverse factor (non-bulky stage II disease, age > 60 years, performance status of 2, or elevated serum LDH) as defined by the stage-modified IPI (N=60), the 4-year PFS rate was 88%, after a median follow-up of 5 years; the corresponding 4-year OS rate was 92%.[21] In historical comparison, these results were favorable relative to the survival rates for patients treated without rituximab (4-year PFS and OS were 78% and 88%, respectively). The MabThera International Trial (MInT) evaluated the role of rituximab in a phase 3 trial comparing 6 cycles of CHOP-like chemotherapy to 6 cycles of CHOP-like chemotherapy plus rituximab.[22,23] All patients were under the age of 60 years and had 0-1 IPI risk factors. Three quarters of patients had limited stage disease, and RT was included for all extranodal sites of disease or any site greater than 7.5 cm. The trial found a benefit to rituximab-containing chemotherapy with a 6-year OS rate of 90.1%% versus 80% (P = .0004). The 6-year EFS rate (74.3% vs. 55.8%; P < .0001) and PFS rate (80.2% vs. 63.9%; P < .0001) were also significantly higher for patients assigned to chemotherapy plus rituximab compared to chemotherapy alone.[23] In the two GELA studies, intensified chemotherapy [ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) followed by consolidation with methotrexate, etoposide, ifosfamide and cytarabine] with or without rituximab was found to be superior to CHOP with or without rituximab (3 cycles) plus RT in patients with low-risk early-stage disease.[24,25] However, this regimen was also associated with significant toxicity and includes vindesine, which is not available in the United States.

Stage III-IV

R-CHOP-21 chemotherapy has been the standard treatment for patients with advanced stage DLBCL based on the results of the GELA study (LNH98-5) that demonstrated the addition of rituximab to CHOP-21 improved PFS and OS in elderly patients with advanced DLBCL. In this study, elderly patients (age 60–80 years; N=399) were randomized to receive 8 cycles of R-CHOP or CHOP.[26-28] Long-term follow-up of this study showed that PFS (36.5% vs. 20%), DFS (64% vs. 43%), and OS (43.5% vs. 28%) rates were significantly in favor of R-CHOP at a median follow-up of 10 years.[29] These findings have been confirmed in three additional randomized trials including the MabThera International Trial (MInT; 6 cycles of R-CHOP or CHOP) which extended the findings to young patients with 0 or 1 risk factors

according to the IPI,[22,23] the Dutch HOVON and Nordic Lymphoma group study (8 cycles of R-CHOP-14 or CHOP-14) and the ECOG/CALGB study confirming the findings in patients older than 60 years.[30,31] The ECOG/CALGB 9703 study also showed that maintenance rituximab in first remission offered no clinical benefit to patients who received R-CHOP as their induction therapy.[31]

The German High Grade Study Group demonstrated that 6 cycles of dose dense CHOP (CHOP-14) as first-line therapy was superior to 6 cycles of CHOP-21, prior to the introduction of rituximab.[32-34] In the RICOVER 60-trial, the addition of rituximab to 6 or 8 cycles of CHOP-14 (R-CHOP-14) significantly improved clinical outcomes in elderly patients (age 61–80 years) compared to CHOP-14 alone.[35,36] With a median observation time of 82 months, EFS was significantly improved after R-CHOP-14 (*P* <.001) compared with CHOP-14. OS rate was also significantly improved in R-CHOP-14 treated patients. No difference in clinical benefit but increased toxicity was seen in patients treated with 8 cycles compared with 6 cycles of therapy.[36] The investigators concluded that 6 cycles of R-CHOP-14 in combination with 8 doses of rituximab should be the preferred regimen in this patient population.

Two randomized trials have now reported data comparing R-CHOP-21 with dose-dense R-CHOP-14.[37,38] A large phase III randomized trial involving 1080 patients with newly diagnosed DLBCL found no significant difference in either PFS or OS at a median follow up of 46 months.[37] The 2-year OS rate was 82.7% in the R-CHOP-14 arm and 80.8% in the R-CHOP-21 arm (*P* = ·3763). The corresponding 2-year PFS rates were 75·4% and 74·8%, respectively (*P* =·5907). Toxicity was similar, except for a lower rate of grade 3 or 4 neutropenia in the R-CHOP-14 arm (31% vs. 60%), reflecting that all patients in the R-CHOP-14 arm received primary growth factor prophylaxis with G-CSF whereas no primary prophylaxis was given with R-CHOP-21.[37] Notably, there was no difference in outcome between GCB-like and non-GCB-like DLBCL by IHC in this large prospective study. The phase III LNH03-6B GELA study compared 8 cycles of R-CHOP-14 with R-CHOP-21 in 602 elderly patients (age 60–80 years) with untreated DLBCL. After a median follow-up of 56 months, no significant differences between R-CHOP-14 and R-CHOP-21 were observed in terms of 3-year EFS (56% vs. 60%; *P* =.7614), PFS (60% vs. 62%) or OS rates (69% vs 72%).[38] Grade 3 or 4 neutropenia were observed more frequently in the R-CHOP-14 arm (74% compared to 64% in the R-CHOP 21 arm) despite a higher proportion of patients having received G-CSF (90%) compared with patients in the R-CHOP-21 arm (66%). Collectively, these studies suggest that R-CHOP-21 remains the standard treatment regimen for patients with newly diagnosed DLBCL with no improvement in outcome observed for dose-dense therapy in the rituximab era.

Very elderly patients (over the age of 80 years) have not been represented in prospective clinical trials of R-CHOP and are usually not appropriate candidates for full-dose therapy. To address this, the GELA study group conducted a multicenter single-arm prospective phase II study evaluating the safety and efficacy of a decreased dose of CHOP with a conventional dose of rituximab (R-mini-CHOP) in 149 patients older than 80 years with DLBCL.[39] After a median follow-up of 20 months, the median OS and PFS were 29 months and 21 months respectively. The 2-year OS and PFS rates were 59% and 47% respectively. An update with extended follow-up reports the 4-year PFS and OS rates to be 41% and 49%, respectively.[40] Grade ≥3 neutropenia was the most frequent hematological toxicity observed in 59 patients. The guidelines have included R-miniCHOP as a treatment option for elderly patients older than 80 years.

Dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) has shown significant activity in untreated patients with DLBCL.[41,42] In a multicenter phase II CALGB study, DA-EPOCH-R (6–8 cycles) was evaluated in patients with previously untreated DLBCL (N=69; included patients with PMBL, n=10).[43] IPI score was high-intermediate risk in 19% and high risk in 21% of patients. After a median follow up of 62 months, the 5-year TTP was 81% and OS was 84% in all patients. The 5-year TTP rates among patients with low/low-intermediate, high-intermediate, and high risk IPI were 87%, 92%, and 54%, respectively (*P* =.0085); the 5-year OS in these subgroups were 95%, 92%, and 43%, respectively (*P*<.001).[43] The TTP rate was significantly higher in the subgroup with GC phenotype compared with non-GC phenotype (100% vs. 67%; *P*=.008); the GC phenotype was also associated with a higher 5-year OS rate (94% vs. 68%; *P*=0.04). High tumor proliferation index (Ki-67 ≥60%) was associated with significantly decreased TTP and OS only for the subgroup with non-GCB phenotype. Febrile neutropenia occurred in 36% (grade 4 in 7%) and no significant grade 4 non-hematologic toxicities were observed. The most common grade 3 non-hematologic toxicities included neuropathies (25%), fatigue (16%), and arrhythmia (6%).[43] An ongoing phase III randomized CALGB study (CALGB 50303) is evaluating DA-EPOCH-R compared with R-CHOP in untreated patients with DLBCL. Pending results of that study, there is insufficient evidence to recommend DA-EPOCH-R as standard initial therapy of newly-diagnosed DLBCL except in highly selected circumstances such as poor left-ventricular function, B-cell lymphoma unclassifiable with intermediate features between DLBCL and Burkitt lymphoma, and primary mediastinal B-cell lymphoma (PMBL), where it warrants consideration (see Discussion section below for PMBL).[44]

As mentioned earlier, standard treatments do not exist for patients with "double-hit" lymphomas with concurrent *MYC* rearrangement and t(14;18) translocation leading to *BCL2* rearrangement. These lymphomas are highly aggressive with poor outcomes with standard DLBCL regimens such as R-CHOP.[11,12] In a series of 193 patients with DLBCL uniformly treated with standard R-CHOP, the median OS (13 months vs. 95 months) and PFS (6 months vs. 95 months), 3-year PFS rate (46% vs. 65%: *P*=.012) and 3-year OS rate (46% vs. 75%; *P*=.002) were significantly lower in patients with "double-hit" lymphoma compared with those without double-hit lymphoma.[11] In another study with a longer follow-up, 5-year PFS and OS were 18% and 27%, respectively, in patients with "double-hit" DLBCL treated with R-CHOP.[12] These studies have also shown that high expressions of both MYC and BCL2 protein levels (assessed by IHC)—but not *MYC* or *BCL2* expression alone—were associated with significantly inferior outcomes after treatment with R-CHOP.[11,12] In the multivariate analysis that included IPI score and cell of origin, concurrent *MYC/BCL2* expression remained a significant independent predictor of poorer PFS and OS after R-CHOP.[11,12]

In a recent multicenter retrospective analysis of 106 patients (77% of patients had "double-hit" lymphomas characterized by *MYC* and *BCL2* rearrangements), R-EPOCH resulted in superior complete responses compared to R-CHOP (*P* = .01) or other intensive induction regimen (*P* = .07).[45] In addition, primary refractory disease occurred less frequently in patients treated with R-EPOCH compared to R-CHOP (*P* = .005) or other intensive indiction regimens (*P* = .03). Prospective studies are needed to evaluate the efficacy of R-EPOCH as well as other regimens and stem cell transplantation strategies in patients with "double-hit" lymphomas. Alternative treatment strategies are needed to improve outcomes in this poor-risk patient population.

NCCN Recommendations

For patients with non-bulky (<10 cm) stage I or II disease, R-CHOP (3 cycles) with IFRT or R-CHOP (6 cycles) with or without IFRT is recommended. IFRT is recommended for patients who are not candidates for chemotherapy. Patients with bulky disease (10 cm or greater) may be more effectively treated with 6 cycles of R-CHOP with or without locoregional RT (category 1).

For patients with advanced stage disease, treatment with R-CHOP-21 (category 1) is recommended. In selected cases, RT to bulky sites may be beneficial (category 2B). R-CHOP-21 is recommended as initial therapy; however, other comparable anthracycline-based regimens may also be acceptable in selected circumstances. Suggested alternate options include dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab (category 2B) or dose-dense R-CHOP-14 (category 3).

The NCCN Guidelines have included the following regimens as first-line therapy options for very frail patients or those with poor left ventricular function:

- R-miniCHOP (for frail patients over 80 years of age)[39,40]
- CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) + rituximab [46]
- CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) + rituximab [47-49]
- CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisone) + rituximab [50-53]
- Dose adjusted EPOCH + rituximab[41,42]
- CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) + rituximab[54]

Participation in clinical trials of new regimens is recommended, if available. In patients with bulky disease or impaired renal function, initial therapy should include monitoring and prophylaxis for tumor lysis syndrome.

Some patients are at increased risk for developing CNS relapse, including those with involvement of the paranasal sinus, testes, bone marrow with large cell lymphoma, or having two or more extranodal sites with elevated LDH.[55-58] Although the optimal management of these patients is still under investigation, the NCCN Guidelines currently recommend CNS prophylaxis with 4 to 8 doses of intrathecal methotrexate and/or cytarabine, or 3-3.5 g/m^2 of systemic methotrexate. For patients with concurrent presentation of parenchymal involvement of the CNS, systemic methotrexate (3–8 g/m^2) should be incorporated as part of the treatment plan; for patients with concurrent leptomeningeal disease, 4 to 8 doses of intrathecal methotrexate and/or liposomal cytarabine and/or 3 to 3.5 g/m^2 systemic methotrexate should be incorporated. When administering high-dose methotrexate, patients should be pre-treated with hydration and alkalinization, and then receive leucovorin rescue beginning 24 hours after the beginning of the methotrexate infusion. Renal and hepatic function must be monitored. Full recovery of blood counts should be confirmed prior to initiating the next cycle of R-CHOP. Systemic methotrexate with leucovorin rescue has been safely incorporated into R-CHOP-21, with methotrexate administered on day 15 of the 21-day R-CHOP cycle.[59]

Response Assessment and Follow-up Therapy

Interim restaging is performed to identify patients whose disease has not responded to or has progressed on induction therapy. PET scans may be particularly useful in determining whether residual masses represent fibrosis or viable tumor. A negative PET scan after 2 to 4

cycles of induction chemotherapy has been associated with favorable outcomes in several studies.[60-63] In patients with aggressive lymphoma (N=90) treated with first-line anthracycline-based induction chemotherapy (with rituximab in 41% of cases), patients with negative PET scans (n=54) after 2 cycles of induction therapy had significantly higher 2-year EFS rate (82% vs. 43%; *P*<0.001) and OS rate (90% vs. 61%; *P*=0.006) compared with those who were PET-positive (n=36).[62] In another study in patients with aggressive lymphoma (N=103) treated with first-line CHOP or CHOP-like regimens (with rituximab in 49% of cases), the 5-year EFS rates were significantly higher for PET-negative patients (n=77) compared to PET-positive patients (n=22) following 4 cycles of induction therapy (80% vs. 36%; *P*<0.0001).[63] However, interim PET scan can produce false positive results and some patients treated with chemoimmunotherapy have a favorable long-term outcome despite a positive interim PET scan. In a prospective study that evaluated the significance of interim PET scans in patients with DLBCL (after 4 cycles of accelerated R-CHOP), only 5 of 37 patients with a positive interim PET scan had a biopsy demonstrating persistent disease; PFS outcome in patients who were interim PET-positive, biopsy-negative was identical to that in patients with a negative interim PET scan.[64] A more recent retrospective analysis (88 newly diagnosed patients with DLBCL treated with 6-8 cycles of R-CHOP) that evaluated the predictive value of interim PET scans on PFS also reported only a minor difference in the 2-year PFS rates between patients with a positive interim PET scan a negative interim PET scan; the 2 year PFS rates were 85% and 72% respectively.[65] Conversely, the end-of-treatment PET scan was highly predictive of PFS; the 2-year PFS rates 83% and 64% respectively for final PET-positive and PET-negative patients (P <.001).

Therefore, interim PET scan is not recommended to be used to guide changes in therapy. If treatment modifications are considered based on interim PET scan results, a repeat biopsy of residual masses is recommended to confirm true positivity. Patients who are receiving induction therapy should undergo evaluation prior to receiving RT, including all positive studies, after 3-4 cycles of chemotherapy. End of treatment restaging is performed upon completion of treatment. The optimal time to end of treatment restaging is not known. However, the panel recommends waiting for 6-8 weeks after completion of therapy before repeating PET scans.

Considerable debate remains with the routine use of imaging for surveillance in patients who achieve a CR after induction therapy. Although positive scans can help to identify patients with early asymptomatic disease relapse, false positive cases remain common and problematic, and may lead to unnecessary radiation exposure for patients as well as increased healthcare costs. In a study that evaluated the use of surveillance CT scans (at 3 and 12 months after completion of chemotherapy) in patients with DLBCL who achieved a CR with induction chemotherapy (N=117), 35 patients relapsed, and only 6% of these relapses were detected by follow-up CT scan in asymptomatic patients; 86% of cases of relapse were associated with development of new symptoms or signs of relapse.[66] The investigators therefore concluded that routine surveillance with CT scans had limited value in the detection of early relapse in patients with a CR following induction therapy. In a retrospective study evaluating the use of surveillance imaging in patients with relapsed aggressive lymphoma who had a CR to initial chemotherapy (N=108), 20% of relapses were detected by imaging in asymptomatic patients.[67] In the remaining 80% of cases, relapse was identified by clinical signs and/or symptoms. Moreover, the cases of relapse detected by imaging were more likely to represent a

population of patients with low-risk disease based on age-adjusted IPI at the time of relapse.[67] Thus, routine imaging during remission may help to identify patients with more limited disease at the time of relapse, but has not been shown to improve ultimate outcome.

In a prospective study that evaluated the role of PET scans (at 6, 12, 18, and 24 months after completion of induction therapy) in patients with a CR after induction therapy for lymphomas, surveillance using PET scans was found to be useful for detecting early relapse.[68] Among the cohort of patients with aggressive lymphomas in this study (n=183), follow-up PET scans detected true relapses in 10% of patients at 6 months, 5% at 12 months, and 11% at 18 months; the rate of false-positive scans was low, at 1% (including cohorts of patients with indolent and aggressive NHL).[68] Inconclusive PET scans were obtained in 8 of 183 cases (4%), 6 of which were confirmed as relapses based on biopsy evaluation. In a retrospective study that evaluated the use of follow-up PET/CT scan in patients with DLBCL who achieved a CR after induction therapy (N=75), follow-up PET/CT scan detected relapse in 27 patients, of which 23 were confirmed as relapses based on biopsy evaluation; thus, the positive predictive value of PET/CT scan for detecting relapse was 0.85.[69] In this study, patient age (>60 years) and the presence of clinical signs of relapse were significant predictors of disease relapse.[69]

Data from more recent retrospective studies also suggest that routine surveillance with PET or CT scans is of limited utility in the detection of relapse in majority of patients with DLBCL. A study comparing the performance of surveillance PET scans in patients with DLBCL treated with CHOP alone versus R-CHOP, found higher false positive results in patients treated with R-CHOP (77% vs. 26%; P < .001).[70] Another study reported a positive predictive value of 56% for surveillance PET-CT scans in patients IPI score <3 compared with 80% for patients with IPI score ≥3, suggesting that surveillance PET-CT has a very limited role in the majority of patients in CR after primary therapy.[71] Another recent multi-institutional retrospective study that evaluated the utility of surveillance scans in a prospective, cohort of 537 patients with DLBCL treated with anthracycline-based chemoimmunotherapy reported that post treatment surveillance scans detected DLBCL relapse prior to clinical manifestations only in 1.5% (8 out 537 patients) during a planned follow-up visit.[72]

In the absence of evidence demonstrating an improved outcome favoring routine surveillance imaging for the detection of relapse, the NCCN Guidelines do not recommend the use of PET or CT for routine surveillance for patients with stage I-II disease who have achieved a CR to initial therapy For patients with stage III-IV disease who achieve remission to initial therapy, the NCCN Guidelines recommend CT scans no more than once every 6 months for up to 2 years after completion of treatment, with no ongoing routine surveillance imaging after that time, unless it is clinically indicated. When surveillance imaging is performed, CT scan is preferred over PET/CT for the majority of patients.

Interim and End of Treatment Response Evaluation for Stage I-II

When the treatment plan involves RT after short course therapy, restaging should be undertaken prior to RT including repeat PET scan as the dose of RT will be influenced by the result (see *"Principles of RT"* in the Guidelines). For full course therapy, if interim restaging demonstrates response, the planned course of treatment is completed.

If the interim restaging demonstrates a PR, treatment with a higher dose of RT (see Guidelines section on "Principles of RT") is appropriate. Alternatively, a repeat biopsy can be obtained and if positive, the patient can proceed to second-line therapy followed by HDT/ASCR. It is appropriate to enroll patients with an interim PR on a clinical trial. The

choice between these two options is often made on clinical grounds. RT is appropriate for patients not eligible for HDT/ASCR. Higher dose RT is also a reasonable choice if there is a very good PR. Patients with refractory or primarily progressive disease are managed as refractory or relapsed disease.

End of treatment restaging is performed upon completion of treatment. Imaging scans for restaging should be obtained at least 6 to 8 weeks after the completion of treatment. After end of treatment restaging, follow-up at regular intervals (every 3–6 months for 5 years and then annually or as clinically indicated thereafter) is recommended for patients with CR. In these patients, follow-up CT scans are recommended only if clinical indicated. Patients with PR and those with no response to treatment or progressive disease are treated as described for relapsed or refractory disease.

Interim and End of Treatment Response Evaluation for Stage III-IV

If interim staging (after 2–4 cycles of R-CHOP-21) demonstrates a CR and PR, the planned course of R-CHOP to a total of 6 cycles is completed. End of treatment restaging is performed upon completion of treatment. Imaging scans for restaging should be obtained approximately 6 to 8 weeks after the completion of treatment. Observation is preferred for patients with CR. RT to initially bulky disease (category 2B) or first-line consolidation with HDT/ASCR can be considered in selected high-risk patients (category 2B, see next section on Role of HDT/ASCR Consolidation in First Remission). Patients in CR are followed up at regular intervals (every 3–6 months for 5 years and then annually or as clinically indicated thereafter). In these patients, follow-up imaging CT scans should be performed no more than every 6 months for 2 years after completion of therapy, and then only as clinically indicated thereafter. Patients with PR (after completion of initial therapy) and those with no response to treatment or progressive disease are treated as described below for relapsed or refractory disease.

Role of HDT/ASCR Consolidation in First Remission

In the randomized GELA LNH87-2 study, patients with DLBCL in first CR after induction therapy received consolidation therapy with either sequential chemotherapy or HDT/ASCR.[73] Although no difference in outcome was prospectively observed in this trial, a retrospective subset analysis of patients with aaIPI high/intermediate- or high-risk disease (n=236), found that HDT/ASCR resulted in significantly improved outcomes compared with sequential chemotherapy with regards to both 8-year disease-free survival rate (55% vs. 39%; *P*=0.02) and 8-year OS rate (64% vs. 49%; *P*=0.04) in the high-intermediate/high-risk subset.[73] This study was performed prior to rituximab-containing induction chemotherapy.

Recently, several randomized trials have prospectively evaluated the role of upfront HDT/ASCR after rituximab-containing first-line chemoimmunotherapy. In the French GOELAMS 075 study, patients aged ≤60 years with DLBCL (N=286 evaluable) were randomized to receive 8 cycles of R-CHOP-14 or HDT with rituximab (R-HDT) followed by ASCR.[74] The 3-year PFS rate and OS rate was 76% and 83%, respectively with no significant differences between treatment arms.[74] In a randomized trial of the German High-Grade NHL Study Group, patients aged ≤60 years with aggressive lymphomas (N=262 evaluable) were treated with 8 cycles of CHOEP-14 combined with 6 doses of rituximab (R-CHOEP-14) or 4 cycles of MegaCHOEP combined with 6 doses of rituximab and followed by ASCR (R-MegaCHOEP).[75] No significant differences were observed between the R-CHOEP-14 and R-MegaCHOEP arms for PFS (3-year rate: 74% vs. 70%, respectively) or OS outcomes (3-year rate: 85% vs. 77%, respectively). Among patients with high/intermediate aaIPI (score of 2), EFS (75.5% vs.

63.5%; *P* = .0509) and OS rates (91% vs. 77.1%; *P* = .01) were significantly better with R-CHEOP-14 compared with R-MegaCHOEP.[75]

In the randomized DLCL04 trial of the Italian Lymphoma Foundation, patients aged ≤65 years with DLBCL, 399 patients were randomized to receive rituximab-containing first-line regimens (8 cycles of R-CHOP-14 or 6 cycles of R-MegaCHOP-14) with or without HDT/ASCR.[76] The 3-year PFS rate was significantly higher in the HDT/ASCR groups compared with the non-HDT/ASCR groups (70% vs. 59%; *P*=.010), but the 3-year OS rate was not significantly different between the two groups (81% and 78% respectively; *P* = .556). In addition, no significant differences were observed in the 3-year PFS rates between the two rituximab-based first-line regimens. In the SWOG 9704 trial, patients with high-intermediate/high IPI DLBCL were randomized (N=253) to receive 3 cycles of R-CHOP or HDT/ASCR, following initial remission with 5 cycles of CHOP or R-CHOP induction.[77] The 2-year PFS rate was significantly higher with HDT/ASCR compared with chemoimmunotherapy alone (69% vs. 56%; *P*=0.005); the 2-year OS rates were not significantly different (74% vs. 71%, respectively). On retrospective subset analysis of high IPI patients, however, an OS benefit was observed; in this subgroup, the 2-year PFS rate with HDT/ASCR was 75% compared with 41% with chemoimmunotherapy; the 2-year OS rate was 82% and 63%, respectively.[77]

The above studies, overall, found no benefit to upfront HDT/ASCR as compared with first-line rituximab-based chemoimmunotherapy. The suggestion of benefit limited to high-IPI risk patients warrants further prospective evaluation. Presently, upfront HDT/ASCR is recommended only in selected high-risk circumstances (category 2B), or in the context of a clinical trial.

Relapsed or Refractory Disease

The role of HDT/ASCR in patients with relapsed or refractory disease was demonstrated in an international randomized phase III trial (PARMA study).[78] In this study, patients with DLBCL responding to induction DHAP (dexamethasone, cisplatin and cytarabine) chemotherapy after first or second relapse (N=109) were randomized to receive additional DHAP chemotherapy plus RT or RT plus HDT/ASCR. The 5-year EFS rate was significantly higher among the transplant group compared with the non-transplant group (46% vs. 12%; *P*=.001), as was the 5-year OS (53% vs. 32%; *P*=.038).[78] This study was performed prior to the availability of rituximab. A recent retrospective analysis based on data from the EBMT registry evaluated the role of HDT/ASCR in patients achieving a second CR after salvage therapy (N=470).[79] In this analysis 25% of patients had received rituximab-containing therapy prior to ASCR. The 5-year DFS and OS was 48% and 63% after ASCR for all patients. The median DFS after ASCR was 51 months, which was significantly longer than the duration of first CR (11 months; *P*<.001). The longer DFS with ASCR compared with first CR was also significant in the subgroup of patients previously treated with rituximab (median not reached vs. 10 months; *P*<.001) and the subgroup who relapsed within 1 year of first-line therapy (median 47 months vs. 6 months; *P*<.001).[79]

The efficacy of second-line therapy is predicted by the second-line age-adjusted IPI.[80,81] Furthermore, pre-transplantation PET scans have been identified as predictive factors following HDT/ ASCR.[82,83] PET positivity before transplant and chemoresistance are associated with a poor outcome.[84,85] The results of studies from the GEL-TAMO group and ABMTR suggested that HDT/ASCR should be considered for patients who do not achieve a CR but who are still sensitive to chemotherapy.[86-88]

Several chemotherapy regimens have been evaluated as second-line therapy prior to HDT/ASCR in patients with relapsed or refractory DLBCL.[89-94] However, none of these have emerged as a preferred regimen. In an outpatient setting, rituximab in combination with ifosfamide, carboplatin and etoposide (R-ICE) produced an ORR of 71% (25% CR) and an estimated 1-year EFS rate and OS rate of 60% and 72%, respectively, in patients with refractory B-cell lymphoma (N=28).[92] In a phase II study, R-ICE regimen produced a CR rate of 53% in patients with relapsed or refractory DLBCL (N=34), which was significantly better than historical controls treated with ICE alone (27%).[93] Rituximab in combination with gemcitabine-based chemotherapy regimens has also been shown to be effective in patients with relapsed or refractory DLBCL.[95-98] Rituximab as a single agent is modestly active in patients with relapsed or refractory DLBCL and is reserved for the frail elderly patient.[99]

An international randomized intergroup study (CORAL study; N=477) evaluated second-line therapy of relapsed or refractory DLBCL with R-ICE versus R-DHAP, followed by ASCR in all chemosensitive patients.[100,101] No significant difference in outcome was found between treatment arms. The overall response rates were 63% after R-ICE and 64% after R-DHAP. The 4-year EFS rate was 26% with R-ICE compared with 34% with R-DHAP (*P* = *.2*) and the 4-year OS rate was 43% and 51%, respectively (*P* = *.3*).[101] Thus, both regimens remain acceptable options for patients with relapsed or refractory DLBCL. Notably, patients relapsing less than 1 year after initial R-CHOP therapy had a particularly poor outcome with 3-year PFS of 23%. Moreover, the subgroup of patients with *MYC* rearrangements (with or without concurrent rearrangements in *BCL2* and/or *BCL6*) had poor outcomes regardless of treatment arm.[102] The 4-year PFS was 18% among patients with *MYC* rearrangements compared with 42% in those without (*P*=.032); 4-year OS was 29% and 62%, respectively (*P*=.011). Among patients with *MYC* rearrangements, the 4-year PFS was 17% with R-DHAP and 19% with R-ICE; OS was 26% and 31%, respectively.[102] Novel approaches are needed for these poor-risk patients. Interestingly, a subgroup analysis from the CORAL study (Bio-CORAL) showed that for patients with a GC phenotype (based on Hans algorithm), R-DHAP resulted in improved PFS (3-year PFS 52% vs. 31% with R-ICE).[103] This difference was not observed among patients with non-GC phenotype (3-year PFS 32% with R-DHAP vs. 27% with R-ICE).[103]

The CORAL study was also designed to evaluate the role of rituximab maintenance (every 2 months for 1 year) following ASCR. Among the patients randomized post-ASCR to rituximab maintenance or observation (n=242), the 4-year EFS (after ASCR) was similar between randomized groups: 52% with rituximab versus 53% with observation.[101] The proportion of patients with progression or relapse was similar between randomized groups. In addition, the 4-year OS was not statistically different (61% and 65%, respectively). Serious adverse events were more frequent in the rituximab maintenance arm. Given that this study showed no benefit with rituximab maintenance compared with observation post-ASCR, maintenance therapy cannot be recommended in this setting.[101]

For patients with relapsed/refractory DLBCL not eligible for transplant, or relapsed after transplant, bendamustine in combination with rituximab (BR) has been evaluated in several studies with encouraging results. In a small dose-escalation study of BR in patients with relapsed/refractory aggressive NHL (N=9; DLBCL, n=5), the 90 mg/m^2 dose of bendamustine (n=3) in the BR regimen resulted in PR in 1 patient while the 120 mg/ m^2 dose of bendamustine (n=6) resulted in CRs in 5 patients and a PR in 1 patient.[104] In elderly patients with relapsed/refractory DLBCL (59 patients; median age 74 years; 48

evaluable patients), the BR combination (with bendamustine dose 120 mg/m^2) resulted in an ORR of 45.8% (15.3% CR; 30.5% PR).[105] The median duration of response and median PFS were 17.3 months and 3.6 months respectively. Myelosuppression was the most common grade 3 or 4 toxicity. In a recent phase II study of the BR regimen (with bendamustine dose 120 mg/m^2) in patients with relapsed/refractory DLBCL (N=59; median age 67 years), the ORR was 63% with a CR in 37% of patients.[106] Patients had received 1 to 3 prior therapies, and were not considered suitable for (or have undergone) ASCR. Nearly all patients (97%) had received prior therapy with rituximab-containing regimens.[106] The median PFS with the BR regimen was approximately 7 months. The most common grade 3 or 4 toxicities were myelotoxicities including neutropenia (76%) and thrombocytopenia (22%).[106]

The regimen of rituximab, gemcitabine and oxaliplatin (R-GemOx) has also been evaluated in patients with relapsed or refractory DLBCL who are not eligible for transplant.[107-109] In a pilot study of 46 patients with relapsed or refractory B-cell lymphoma, the majority of whom (72%) had DLBCL, R-GemOx resulted in an ORR of 83% and half of the patients achieved a CR.[107] The 2-year EFS and OS rates in this study were 43% and 66%, respectively. In a subsequent multicenter phase II study that included 49 patients with relapsed or refractory DLBCL, R-GemOx resulted in an ORR of 61% (44% CR and 17% PR).[109] The 5-year PFS and OS rates were 12.8% and 13.9%, respectively.

NCCN Recommendations

HDT/ASCR is the treatment of choice for patients with relapsed or refractory disease that is chemosensitive at relapse. Patients with relapsed or refractory DLBCL who are candidates for HDT/ASCR should be treated with second-line chemotherapy, with or without rituximab (depending on whether the patient is deemed to be refractory to prior rituximab regimens). Suggested regimens (with or without rituximab) include the following:

- DHAP (dexamethasone, cisplatin, cytarabine),
- ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin)
- GDP (gemcitabine, dexamethasone, cisplatin)
- GemOx (gemcitabine and oxaliplatin)
- ICE (ifosfamide, carboplatin and etoposide)
- MINE (mitoxantrone, ifosfamide, mesna, etoposide)

Patients with CR or PR to second-line chemotherapy regimen should be considered for further consolidation with HDT/ASCR (category 1 for patients with CR) with or without RT. IFRT before HDT/ASCR has been shown to result in good local disease control and improved outcome.[110] Additional RT can be given before or after stem cell rescue to sites with prior positive disease. Pertinent clinical trials, including the option of allogeneic stem cell transplantation, may also be considered.

Patients who are not eligible for HDT/ASCR should be treated in the context of a clinical trial. Alternatively, in the absence of suitable clinical trials, patients can also be treated with single-agent rituximab, bendamustine with or without rituximab,[111] lenalidomide (in patients with non-germinal center DLBCL) with or without rituximab[112-116] or multiagent chemotherapy regimens (with or without rituximab) such as dose-adjusted EPOCH,[117,118] CEPP (cyclophosphamide, etoposide, prednisone and procarbazine),[46] GDP [95,119] or GemOx.[107-109]

Patients with disease relapse following HDT/ ASCR should be treated in the context of a clinical trial or treatment should be individualized. However, those with progressive disease after three successive regimens are unlikely to derive additional benefit from currently available chemotherapy regimens, except for patients who have

experienced a long disease-free interval. All patients with relapsed or refractory DLBCL should be considered for enrollment in available clinical trials.

Primary Mediastinal Large B-cell Lymphoma (PMBL)

PMBL is a distinct subtype of NHL that histologically can be indistinguishable from DLBCL. This subtype tends to occur in young adults with a median age of 35 years with a slight female predominance.[120,121] PMBL arises from thymic B-cells with initial local regional spread to supraclavicular, cervical, hilar nodes and into the mediastinum and lung.[120] Widespread extranodal disease is uncommon at initial diagnosis, present in approximately one quarter of patients, but can be more common at recurrence.[121] Clinical symptoms related to rapid growth of mediastinal mass include superior vena cava (SVC) syndrome, pericardial and pleural effusions.

Gene expression profiling has indicated that PMBL is distinct from DLBCL; the pattern of gene expression in PMBL is more similar to classical Hodgkin lymphoma (CHL).[122,123] PMBL expresses B-cell antigens and lacks surface immunoglobulins. PMBL is CD19+, CD20+, CD22+, CD21-, IRF4/MUM1+ and CD23+ with a variable expression of BCL2 and BCL6. CD30 is weakly and heterogeneously expressed in more than 80% of cases and CD15 is occasionally present.[121] CD10 positivity is seen in 8-32% cases. PMBL is also characterized by a low expression of HLA I or II molecules. There have been rare cases of mediastinal gray zone lymphomas with combined features of PMBL and CHL. Cytogenetic abnormalities that are common in PMBL include gains in chromosome 9p24 (involving the *JAK2* in 50–75% of patients) and chromosome 2p15 (involving the *c-REL*, encoding a member of the NF-κB family of transcription factors) and loss in chromosomes 1p, 3p, 13q, 15q, and 17p. [121] Age-adjusted IPI is of limited value in determining the prognosis of PMBL at diagnosis.[120,124,125] In a retrospective analysis of 141 patients from MSKCC, two or more extranodal sites and the type of initial therapy were predictors of outcome for EFS, whereas only the initial therapy was a predictor for OS.[124]

In retrospective analyses, intensive chemotherapy regimens have appeared more effective than CHOP[125-127] and the addition of IFRT has been associated with improved PFS; however, these studies were conducted in the pre-rituximab era.[128,129] The role of RT requires confirmation in prospective randomized trials. In a retrospective study, the addition of rituximab to MACOP-B or VACOP-B did not appear to result in significant differences in clinical outcomes, but it did appear to improve outcome when added to CHOP.[125,130-132]

A retrospective analysis of 63 patients with PMBL treated with R-CHOP found a 21% rate of primary induction failure, with adverse predictors of outcome being advanced stage and high-risk IPI scores. These data question whether R-CHOP is the optimal chemotherapy backbone in PMBL, particularly for high-risk patients.[133] A small prospective NCI study of the dose-adjusted EPOCH-R regimen (DA-EPOCH-R) without RT demonstrated an encouraging 91% EFS at a median follow-up of 4 years. In a subsequent prospective phase II study from the NCI, DA-EPOCH-R (6–8 cycles) and filgrastim, without RT, was evaluated in 51 patients with previously untreated PMBL.[44] Stage IV disease was present in 29% of patients. After DA-EPOCH-R therapy, 2 patients showed persistent focal disease and 1 patient had disease progression; 2 of these patients required mediastinal RT while 1 patient was observed after excision biopsy. At a median follow up of 63 months, EFS and OS rates were 93% and 97%, respectively. Grade 4 neutropenia and thrombocytopenia occurred in 50% and 6% of treatment cycles, respectively. Hospitalization for febrile neutropenia occurred in 13% of cycles.[44] This study showed that DA-EPOCH-R is a

highly effective regimen in patients with PMBL and obviates the need for RT in the large majority of patients. These observations will ideally be confirmed in larger prospective studies.

In an analysis of the subgroup of patients with PMBL (N=87) from the randomized MInT study, which evaluated CHOP-like regimens with or without rituximab, the addition of rituximab significantly improved the CR rate (80% vs. 54% without rituximab; *P*=.015) and 3-year EFS rate (78% vs. 52%; *P*=.012), but not the OS rate (89% vs. 78%; *P* = .158).[131] In a recent follow-up report with a median observation time of 62 months in patients with PMBL, the increase in EFS with rituximab remained significant at 5 years (79% vs. 47%; *P*=.011).[134] The 5-year PFS was also significantly increased in the rituximab arm (90% vs. 60%; *P*=.006); 5-year OS was not significantly different (90% vs. 78%), but was similar to OS outcomes in patients with DLBCL in this study (92% with rituximab vs. 81% without; *P*<.001).[134] The MInT study, however, only included young low-risk patients with IPI scores 0-1. Sequential dose dense R-CHOP followed by ICE consolidation (without RT) was also highly effective in patients with PMBL, with similar outcomes to the above analysis with R-chemotherapy from the MInT study.[135] At a median follow up for surviving patients at 3 years, the OS and PFS rates were 88% and 78%, respectively.[135]

In the absence of randomized trials, optimal first-line treatment for patients with PMBL is more controversial than other subtypes of NHL. However, based on the available data, the following regimens are included as options for first-line therapy.

- R-CHOP (6 cycles) + RT
- Dose-adjusted R-EPOCH (6 cycles)[44] + RT for persistent local disease
- R-CHOP (4 cycles) followed by ICE (3 cycles)[135] with or without RT (category 2B)

Post-treatment PET-CT is considered essential; if PET-CT is negative at the end of treatment and initial disease was non-bulky, patients may be observed. Residual mediastinal masses are common. For patients initially treated with R-CHOP, consolidation with RT can be considered, particularly if increased FDG-activity persists in the primary tumor. For patients who are PET-CT negative after more intensive therapies (e.g., dose-adjusted EPOCH-R), observation may be appropriate. If PET-CT is positive, biopsy is recommended if additional treatment is contemplated.

Grey Zone Lymphoma

Grey zone lymphomas refer to a group of lymphomas with overlapping histological and clinical features representative of different lymphoma subtypes.[136] In the context of large B-cell lymphomas, grey zone lymphomas fall under the category of "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma (CHL) of the 2008 WHO classification.[134,136-138] Other synonyms include large B-cell lymphoma with Hodgkin features or Hodgkin-like anaplastic large cell lymphoma. Patients with gray zone lymphomas may present with mediastinal or non-mediastinal disease. Clinically, patients with mediastinal grey zone lymphomas present with large anterior mediastinal mass with or without supraclavicular lymph node involvement. These mediastinal lymphomas are more commonly seen in young adult males between the ages of 20 to 40 years.[136,137,139] Patients with non-mediastinal gray zone lymphoma tended to be older and have a higher incidence of advanced stage disease and high-risk IPI score than their mediastinal counterparts.[140] The morphology of grey zone lymphomas is characterized by sheet-like growth of pleomorphic cells in a diffusely fibrous stroma; cells are typically larger

and more pleomorphic than those in PMBL, and may sometimes resemble lacunar or Hodgkin-like cells.[138] Necrosis without neutrophilic infiltration is frequently present.[134,137,138]

The immunophenotype is atypical, often showing transitional features between PMBL and CHL. In general, CD45 is often positive, and CD15, CD20, CD30, and CD79a are also frequently positive. CD10 and ALK are usually negative. B-cell transcription factors such as PAX5, BOB.1, and OCT-2 are often positive.[137,138,141] BCL6 is variably expressed. EBV is more often negative.[136,137] If the morphology more closely resembles PMBL, absence of CD20, CD15 positivity, or presence of EBV would be suggestive of grey zone lymphoma. If the morphology more closely resembles CHL, strong CD20 expression (and/or other B-cell markers) and absence of CD15 would be suggestive of grey zone lymphoma.[137] A study that evaluated epigenetic changes based on DNA methylation analysis of microdissected tumor cells from patients with mediastinal grey zone lymphomas, PMBL, CHL, and DLBCL showed distinct methylation signatures (hypomethylated and hypermethylated sites) of CpG targets between PMBL and CHL.[142] The methylation profiles of patients with grey zone lymphoma were intermediate to those of PMBL and CHL, but distinct from patients with DLBCL. Among 235 CpG targets that were identified as being differentially methylated between the lymphomas, 22 targets could be used to readily distinguish between PMBL and CHL cases, with grey zone lymphomas showing an overlap of both signatures. The investigators concluded that the unique epigenetic signature of mediastinal grey zone lymphomas provide validation of its classification as a separate disease entity in the 2008 WHO classification.[142]

The treatment of patients with grey zone lymphomas poses a challenge, as these lymphomas appear to be associated with a worse prognosis compared with PMBL or CHL.[138,141,143] No standard of care or consensus exists for the management of patients with grey zone lymphomas, although patients are typically treated with multiagent chemotherapy regimens used for patients with DLBCL with the addition of RT for localized disease; some reports suggest that grey zone lymphomas tend to be resistant to chemotherapy regimens used in CHL.[139,144] The addition of rituximab is generally suggested for tumors expressing CD20. In a study that evaluated 6 to 8 cycles of DA-EPOCH-R in a small group of patients with mediastinal grey zone lymphoma (n=11), the 4-year PFS was 30% and 4-year OS was 83%.[144] These outcomes appeared to be poorer compared with the group of patients with PMBL (n=35) in the same study; the 4-year PFS and OS rates were 100% for both endpoints in patients with PMBL treated with DA-EPOCH-R. Moreover, half of the patients with grey zone lymphoma required mediastinal RT.[144] Given the apparent inferior outcomes among gray zone lymphomas treated with traditional chemotherapy regimens, consolidative RT should be strongly considered for patients with limited stage disease amenable to RT.

Patients with grey zone lymphomas are best managed in cancer centers with experience in treating this type of lymphoma, preferably in the context of clinical trials where appropriate. In the absence of suitable clinical trials, an intensive regimen such as DA-EPOCH-R (with mediastinal RT, as needed, for local disease) may be considered.

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