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Diffuse Large B-Cell Lymphoma Version 1.2016

Clinical Practice Guidelines in Oncology

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Overview

Diffuse large B-cell lymphomas (DLBCL) are the most common lymphoid neoplasms in adults, accounting for approximately 32.5% of non-Hodgkin's lymphoma (NHL) cases diagnosed annually.[1] Gene expression profiling (GEP) has revealed significant heterogeneity within DLBCL.[2] Immunohistochemi-

Abstract

Diffuse large B-cell lymphomas (DLBCL) are now considered a heterogeneous group of distinct molecular subtypes (germinal center B-cell DLBCL, activated B-cell DLBCL, and primary mediastinal large B-cell lymphoma (PMBL) with varied natural history and response to therapy. In addition, a subset of patients with DLBCL have concurrent *MYC* and/or *BCL2* gene rearrangements (double-hit lymphomas; DHL) and others have a dual expression of both MYC and BCL2 proteins (double-expressing DLBCL; DEL). The standard of care for the treatment of patients with PMBL, DHL, or DEL has not been established. Adequate immunophenotyping and molecular testing (in selected circumstances) are necessary for the accurate diagnosis of different subtypes of DLBCL. The NCCN Guidelines included in this issue, part of the NCCN Guidelines for non-Hodgkin's lymphomas, address the diagnosis and management of DLBCL and its subtypes.

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Non-Hodgkin's Lymphomas are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the NCCN Non-Hodgkin's Lymphomas Oncology Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Non-Hodgkin's Lymphomas Panel members can be found on pages 230 and 231. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

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cal markers such as CD10, BCL6, and IRF4/MUM1 have been reported to recapitulate GEP in classifying DLBCL into 2 different subtypes: germinal center B-cell (GCB) subtype and non-GCB subtype.[3] Immunohistochemical algorithms including GCET1, FOXP1, and LMO2 in addition to CD10, BCL6, and IRF4/MUM1 have also been proposed.[4,5] However, incorporation of this information into treatment algorithms awaits further investigation. MYC gene rearrangements have been reported in 5% to -8% of patients with DLBCL and often correlate with GCB phenotype.[6–8] GCB subtype is associated with an improved outcome compared with non-GCB subtype in patients treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Ongoing clinical trials are exploring whether the addition of novel targeted agents to R-CHOP will selectively improve the outcome in patients with non-GCB DLBCL.[9,10]

Currently, the upfront standard of care remains the same for both GCB and non-GCB subtypes.

Diagnosis

Adequate immunophenotyping is required to establish the diagnosis and to determine GCB versus non-GCB origin. The recommended immunophenotyping panel includes CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF4/MUM1, and MYC. Additional markers such as CD138, CD30, cyclin D1, ALK1, SOX11, EBV, and HHV-8 may be useful under certain circumstances to establish the subtype. Patients with GCB-like immunophenotype along with the expression of MYC and either BCL2 or BCL6 by immunohistochemistry (IHC) should

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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 with or without
  - 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, Epstein-Barr virus in situ hybridization (EBER-ISH), ALK, HHV8, SOX11
- Karyotype or FISH: *MYC, BCL2, BCL6* rearrangements[e]

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 Central Nervous System Cancers, available at NCCN.org)

Primary Mediastinal Large B-Cell Lymphoma (PMBL), see BCEL-B 1 of 3.
Grey Zone Lymphoma, see BCEL-B 2 of 3.
Double Hit Lymphomas, see BCEL-B 3 of 3.

*Available in the full version of these guidelines at NCCN.org.

[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*.

[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]Cases with double expression of MYC and either BCL2 or BCL6 by IHC having a GCB-like immunophenotype should undergo FISH testing for *MYC, BCL2,* and *BCL6* rearrangement.

[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.

BCEL-1

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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
- PET-CT scan ± chest/abdominal/pelvic CT with contrast of diagnostic quality
- 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) (See BCEL-A 1 of 2)
- Hepatitis B testing[h]
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
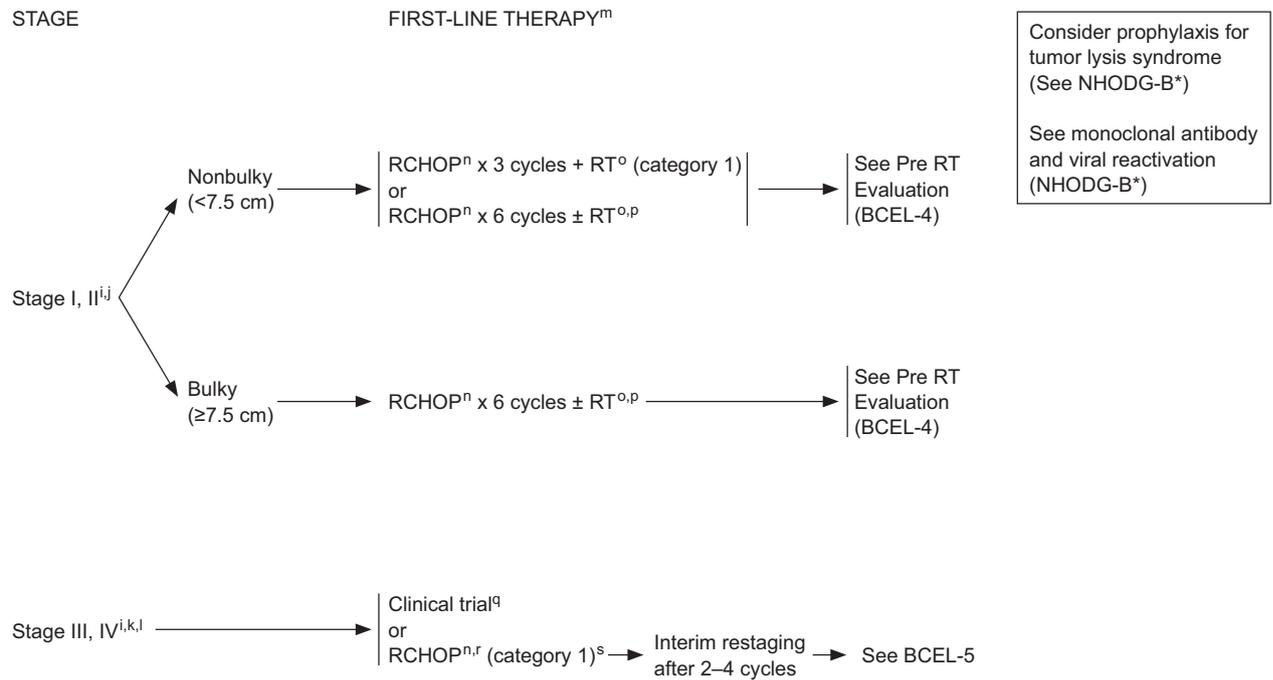- Pregnancy testing in women of child-bearing age

USEFUL IN SELECTED CASES:
- Neck CT, head CT, or MRI
- Discussion of fertility issues and sperm banking
- HIV
- Lumbar puncture, consider if have 4–6 factors according to prognostic model (See BCEL-A 2 of 2), HIV lymphoma, testicular, double expressor lymphoma
- Beta-2-microglobulin

→ See Induction Therapy (BCEL-3)

[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.

BCEL-2

STAGE

FIRST-LINE THERAPY[m]

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

See monoclonal antibody and viral reactivation (NHODG-B*)

Stage I, II[i,j]

Nonbulky (<7.5 cm) → RCHOP[n] x 3 cycles + RT[o] (category 1) or RCHOP[n] x 6 cycles ± RT[o,p] → See Pre RT Evaluation (BCEL-4)

Bulky (≥7.5 cm) → RCHOP[n] x 6 cycles ± RT[o,p] → See Pre RT Evaluation (BCEL-4)

Stage III, IV[i,k,l] → Clinical trial[q] or RCHOP[n,r] (category 1)[s] → Interim restaging after 2–4 cycles → See BCEL-5

*Avilable in the full version of these guidelines at NCCN.org.

[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 (4–6 factors according to prognostic model, HIV lymphoma, testicular, double hit lymphoma), 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 to Assess the 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]If RT is not used, interim staging after 3–4 cycles of RCHOP is appropriate to confirm response.
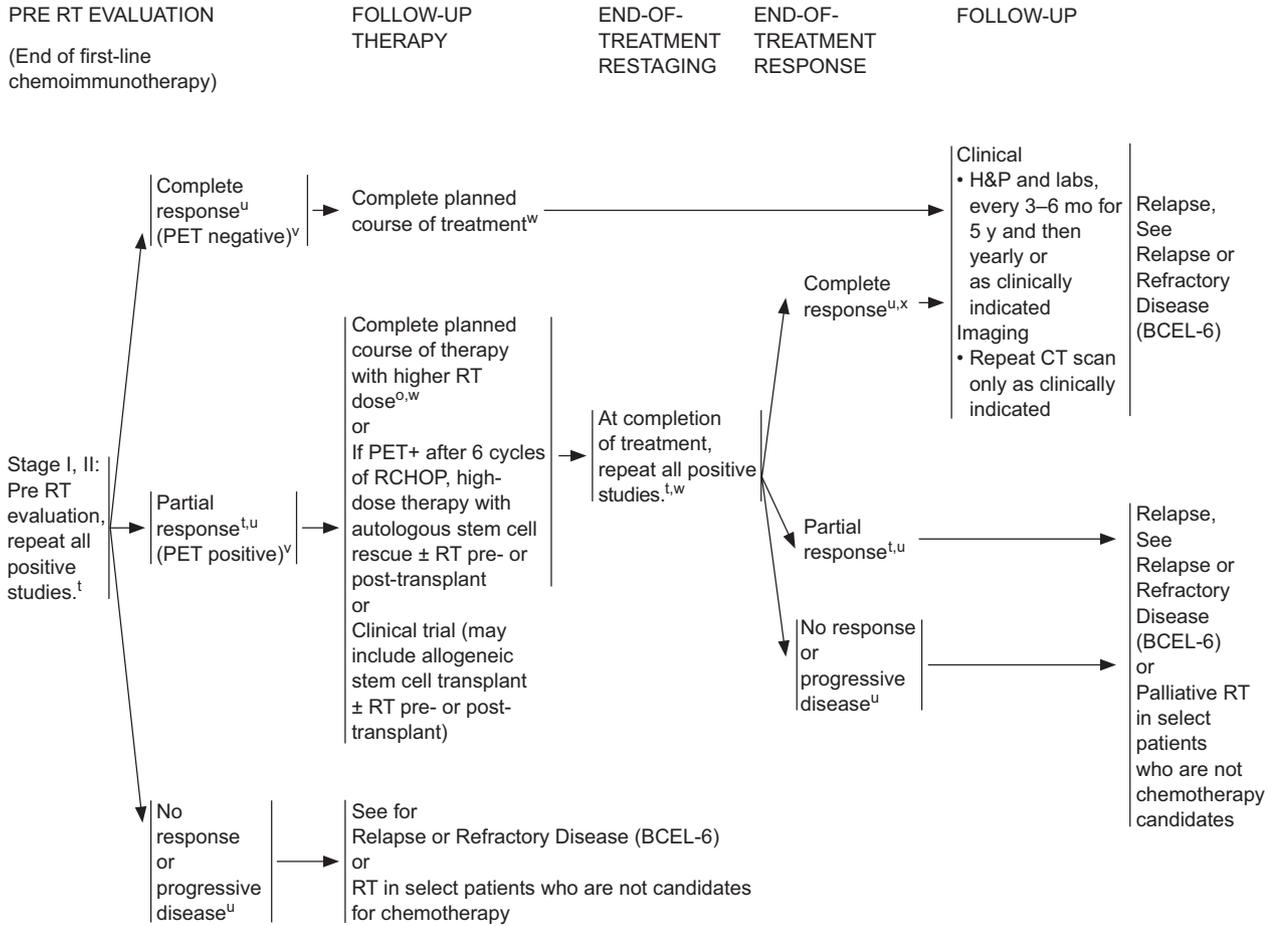
[q]May include high-dose therapy.

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

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

BCEL-3

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PRE RT EVALUATION	FOLLOW-UP THERAPY	END-OF-TREATMENT RESTAGING	END-OF-TREATMENT RESPONSE	FOLLOW-UP

(End of first-line chemoimmunotherapy)

Stage I, II: Pre RT evaluation, repeat all positive studies.[t]

Complete response[u] (PET negative)[v] → Complete planned course of treatment[w] → Clinical
• H&P and labs, every 3–6 mo for 5 y and then yearly or as clinically indicated
Imaging
• Repeat CT scan only as clinically indicated → Relapse, See Relapse or Refractory Disease (BCEL-6)

Partial response[t,u] (PET positive)[v] → Complete planned course of therapy with higher RT dose[o,w]
or
If PET+ after 6 cycles of RCHOP, high-dose therapy with autologous stem cell rescue ± RT pre- or post-transplant
or
Clinical trial (may include allogeneic stem cell transplant ± RT pre- or post-transplant) → At completion of treatment, repeat all positive studies.[t,w]

At completion of treatment, repeat all positive studies.[t,w] →
- **Complete response[u,x]** → Clinical follow-up (as above) → Relapse, See Relapse or Refractory Disease (BCEL-6)
- **Partial response[t,u]** → Relapse, See Relapse or Refractory Disease (BCEL-6) or Palliative RT in select patients who are not chemotherapy candidates
- **No response or progressive disease[u]** → Relapse, See Relapse or Refractory Disease (BCEL-6) or Palliative RT in select patients who are not chemotherapy candidates

No response or progressive disease[u] → See for Relapse or Refractory Disease (BCEL-6) or RT in select patients who are not candidates for chemotherapy

*Available in the full version of these guidelines at NCCN.org.

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

[t]Repeat biopsy should be strongly considered if PET positive prior to additional therapy. If biopsy negative, follow PET-negative guideline.

[u]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C*).

[v]PET-CT scan should be interpreted via the PET Five Point Scale (See NHODG-C 3 of 3*).
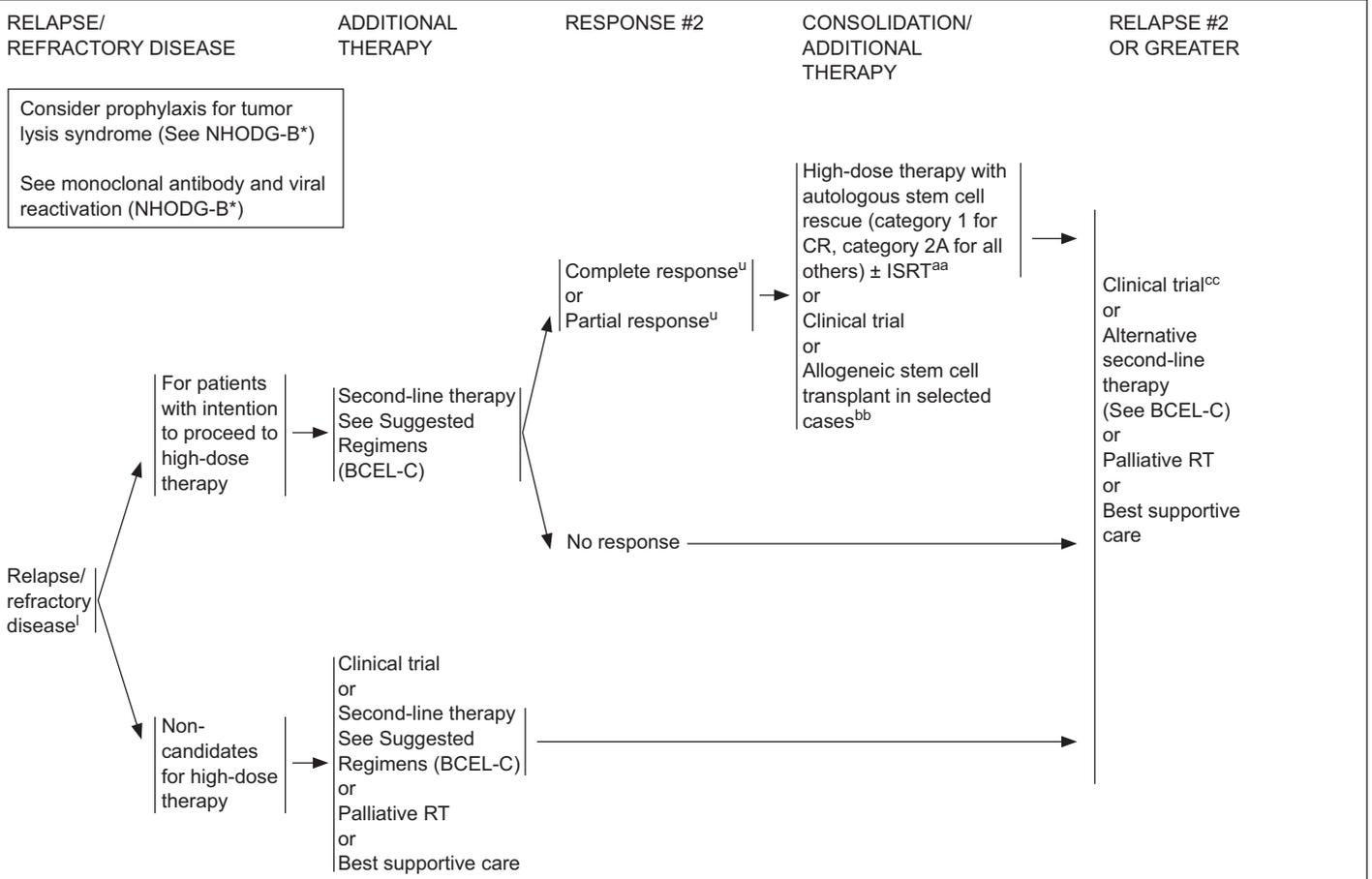
[w]The optimum timing of end-of-treatment PET-CT is unknown; however, waiting a minimum of 8 weeks after RT to repeat PET-CT scan is suggested. False positives may occur due to posttreatment changes.

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

BCEL-4

INTERIM RESTAGING	FOLLOW-UP THERAPY	END-OF-TREATMENT RESTAGING	END-OF-TREATMENT RESPONSE		FOLLOW-UP

Stage III, IV: After 2–4 cycles, restage to confirm response[y]

→ **Responding disease** → Continue RCHOP[y] to a total of 6 cycles (category 1) or Clinical trial → At completion of treatment, repeat all positive studies.[t]

→ **Complete response[u] (PET negative)[v]** → Observation or Consider RT to initially bulky disease or Consider high-dose therapy with autologous stem cell rescue in high-risk patients (category 2B) → Clinical
• H&P and labs, every 3–6 mo for 5 y and then yearly or as clinically indicated
Imaging
• CT scan no more often than every 6 mo for 2 y after completion of treatment, then only as clinically indicated

→ **Partial response[t,u] (PET positive)[v]** → Relapse, See Relapsed or Refractory Disease (BCEL-6) or Palliative RT in select patients who are not candidates for chemotherapy

→ **No response or progressive disease[u]** →

→ **No response or progressive disease[u]** → See Relapse or Refractory Disease (BCEL-6) or RT in select patients who are not candidates for chemotherapy

*Available in the full version of these guidelines at NCCN.org.

[t] Repeat biopsy should be strongly considered in PET positive prior to additional therapy. If biopsy negative, follow PET-negative guideline.

[u] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C*).

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

[y] 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.

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

BCEL-5

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

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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[u] or Partial response[u] → High-dose therapy with autologous stem cell rescue (category 1 for CR, category 2A for all others) ± ISRT[aa] or Clinical trial or Allogeneic stem cell transplant in selected cases[bb]

No response ⟶

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

Non-candidates for high-dose therapy → Clinical trial or Second-line therapy See Suggested Regimens (BCEL-C) or Palliative RT or Best supportive care ⟶

*Available in the full version of these guidelines at NCCN.org.

[l]For systemic disease with concurrent CNS disease, see BCEL-C.
[u]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C*).
[aa]Additional RT can be given before or after high-dose therapy with stem cell rescue to sites of previous positive disease.
[bb]Selected cases include mobilization failures and persistent bone marrow involvement.
[cc]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.

BCEL-6

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

STAGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[b]

STAGE I or II PATIENTS:
- Age >60 years
- Serum LDH > normal
- Performance status 2–4
- Stage II or IIE

INTERNATIONAL INDEX, STAGE I or II PATIENTS:
- Low   0 or 1
- High   2–4

NCCN-IPI[c]

Age, years		Risk group	
>40 to ≤60	1	• Low	0–1
>60 to <75	2	• Low-intermediate	2–3
≥75	3	• High-intermediate	4–5
LDH, normalized		• High	≥6
>1 to ≤3	1		
>3	2		
Ann Arbor stage III-IV	1		
Extranodal disease*	1	*Disease in bone marrow, CNS, liver/GI tract, or lung.	
Performance status ≥2	1		

[a]The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma. N Engl J Med 1993;329:987-994.

[b]Miller TP, Dahlberg S, Cassady JR. 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.

[c]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.

BCEL-A
1 OF 2

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

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Prognostic Model to Assess the Risk of CNS Disease[a,b]

• Age >60 years	Low risk	0–1
• Serum LDH > normal	Intermediate-risk	2–3
• Performance status >1	High-risk	4–6
• Stage III or IV		
• Extranodal involvement >1 site		
• Kidney or adrenal gland involvement		

[a]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.

[b]Savage K, Zeynalova S, Kansara RR, 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:Abstract 394.

BCEL-A
2 OF 2

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 3).

- Clinical pathologic correlation is required to establish diagnosis.

- Optimal first-line therapy is more controversial than other subtypes of NHL; however, treatment regimens include (in order of preference):
  ‣ Dose-adjusted EPOCH-R ([etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab)[a] x 6 cycles
    ◊ for persistent focal disease, RT can be added.
  ‣ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) x 6 cycles + RT
  ‣ 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.

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[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.

BCEL-B
1 OF 3

Diffuse Large B-Cell Lymphoma Version 1.2016

<u>Grey Zone Lymphoma</u>[a,b,c]
<u>(intermediate between DLBCL and classical HL)</u>

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
- Non-mediastinal grey zone lymphoma is more likely compared to mediastinal cases to occur in older individuals and typically have higher risk features, more advanced-stage disease, and higher IPI.[d]

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 -
- PAX5, BOB.1, OCT-2 are often positive, BCL6 variable
- CD10, ALK are negative
- If morphology closer to PMBL, or absence of CD20, CD15+ 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 regimens are preferred.
- 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 is preferred.
- There is no ostensible difference in outcome between mediastinal and non-mediastinal grey zone lymphoma.

[a]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.

[b]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.

[c]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.

[d]Evens AM, Kanakry JA, Sehn LH, et al. Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma: Characteristics, outcomes, and prognostication among a large multicenter cohort. Am J Hematol 2015;90:778-783.

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Double-Hit Lymphomas

Definition
- Double Hit (Double Rearrangements):
  - DLBCL or HGB-NOS (intermediate between DLBCL and BL) with *MYC* rearrangment in addition to *BCL2* and/or *BCL6* rearrangements (as detected by FISH or standard cytogenetics) are known as "double-hit" lymphomas (if all three are rearranged, they are referred to as "triple-hit" lymphomas).
  - Vast majority are germinal center B-cell–like lymphomas

Clinical Presentation
- Often present with poor prognostic parameters, such as elevated LDH, bone marrow and CNS involvement, and a high IPI score.

Treatment
- Clinical trial is recommended.
- While the standard of care is not established, the following regimens have been used at NCCN Member Institutions:
  - DA-EPOCH-R
  - RHyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
  - R-CODOX-M/R-IVAC (rituximab-cyclophosphamide, vincristine, doxorubicin with methotrexate/ifosfamide, etoposide, and cytarabine)
- RCHOP has been associated with inferior outcomes.
- Consider consolidation with high-dose therapy with autologous stem cell rescue. While its role is not established, this is done at some NCCN Member Institutions.

References:

Petrich A, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood 2014;124:2354-2361.

Dunleavy K, Fanale M, LaCasce A, et al. Preliminary report of a multicenter prospective phase II study of DA-EPOCH-R in MYC-rearranged aggressive B-cell lymphoma [abstract]. Blood 2014:Abstract 395.

Johnson NA, Slack GW, Savage KJ et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3452-3459.

Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3460-3467.

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Diffuse Large B-Cell Lymphoma Version 1.2016

SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

First-line Therapy
• RCHOP (rituximab,[b] cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
• Dose-dense RCHOP 14[b] (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[c,d,e]
• RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)
• RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)
• DA-EPOCH[f] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
• RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)
• RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone)

Patients >80 Years of Age with Comorbidities[e]
• R-mini-CHOP
• RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone)

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

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*)

*Available in the full version of these guidelines at NCCN.org.

[a]See references for regimens BCEL-C 3 of 4 and BCEL-C 4 of 4.
[b]In RCHOP-14 and RCHOP-21, may consider increasing dose of rituximab to 500 mg/m^2 in men >60 y.
[c]Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[d]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.
[e]There are limited data for treatment of early stage disease with these regimens; however, short course chemotherapy + RT for Stage I-II disease is practiced at NCCN Member Instituions.
[f]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[c,g,h] (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[c,g,h] (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 or (gemcitabine, dexamethasone, carboplatin) ± rituximab
• GemOx ± rituximab
• Lenalidomide ± rituximab (non-GCB DLBCL)
• 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*)

*Available in the full version of these guidelines at NCCN.org.

[a]See references for regimens BCEL-C 3 of 4 and BCEL-C 4 of 4.
[c]Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.
[g]If additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.
[h]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, Bergua J, Gallur L, et al. Long-term follow-up of dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor prognosis large B-cell lymphoma. A phase II study conducted by the Spanish PETHEMA Group. Br J Haematol 2015;169:188-198.

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.

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.

RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, and prednisolone)

Fields PA, Townsend W, Webb A, et al. De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients with cardiac comorbidity: a United Kingdom National Cancer Research Institute trial. J Clin Oncol 2014;32:282-287.

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.

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.

Vacirca JL, Acs PI, Tabbara IA, et al. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. Ann Hematol 2014;93:403-409.

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
Jacobsen ED, Sharman JP, Oki Y, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. Blood 2015;125:1394-1402.

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.

Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE (RICE) as second-line therapy prior to autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004;103:3684-8.

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.

Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive Non-Hodgkin's lymphoma. J Clin Oncol 2008;26:4952-4957.

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.

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

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undergo fluorescence in-situ hybridization (FISH) or karyotype testing for the detection of MYC, BCL2, and BCL6 gene rearrangements. SOX11 positivity may be useful in differentiating rare cases of cyclin D1-negative pleomorphic or blastoid mantle cell lymphoma from CD5-positive DLBCL.[11,12]

Workup

The initial workup for patients with newly diagnosed disease is outlined in BCEL-2 (see page 199). Patients with high tumor burden and elevated serum lactate dehydrogenase (LDH) should be assessed for spontaneous tumor lysis syndrome, including measurements of uric acid, potassium, phosphorous, calcium, and renal function. Hepatitis B virus testing (surface antigen, surface antibody, and core antibody) is recommended, especially if rituximab-based treatment regimens are being considered, because of increased risks of viral reactivation,[13] although viral reactivation has also been described after chemotherapy alone without rituximab. HIV testing and serum beta-2-microglobulin levels would be useful in selected patients.

PET scans are particularly informative in initial staging and for response assessment after treatment because they can distinguish residual fibrotic masses from masses containing viable tumor.[14] PET-CT scan with or without chest/abdominal/pelvic CT with contrast of diagnostic quality is recommended for initial workup. A baseline PET scan is necessary for optimal interpretation of post-treatment PET scans. PET-CT has also been reported to be accurate and complementary to bone marrow biopsy for the detection of bone marrow involvement in patients with newly diagnosed DLBCL.[15,16] Bone marrow biopsy may not be needed if there is clearly positive marrow uptake by PET-CT. Bone marrow biopsy may also be omitted in the absence of any skeletal uptake on the staging PET/CT scan, unless finding another lymphoma subtype (discordant low-grade lymphoma) would be considered important for treatment decisions.

The staging workup is designed to identify all sites of known disease and determine prognosis with known clinical risk factors.The International Prognostic Index (IPI) identifies specific groups of patients who are more or less likely to be cured with standard therapy.[17,18] IPI scores are based on patient's age, stage of disease, serum LDH level, performance status (PS), and the number of extranodal sites. More recently, an enhanced IPI (NCCN-IPI) has been reported to stratify patients with newly diagnosed DLBCL into 4 different risk groups (low, low-intermediate, high-intermediate, and high) based on age, LDH, sites of involvement, Ann Arbor stage, and ECOG PS.[19] In an analysis of 1650 patients with DLBCL identified in the NCCN database (diagnosed between 2000 and 2010) treated with rituximab-based therapy, the NCCN-IPI discriminated patients in the low- and high-risk subgroups better (5-year overall survival [OS] rate, 96% vs 33%) than the IPI (5 year OS rate, 90% vs 54%). The NCCN-IPI was also validated using an independent cohort of 1138 patients from the British Columbia Cancer Agency. Although the IPI, revised IPI (R-IPI), and NCCN-IPI predict clinical outcome with high accuracy, R-IPI and NCCN-IPI could also identify a specific subgroup of patients with very good prognosis (3-year progression-free survival [PFS] and OS of 100%).[20]

Elevated LDH, 2 or more extranodal sites, and involvement of specific sites (the testes, paranasal sinus and bone marrow) are associated with increased risk for developing central nervous system (CNS) relapse.[21–23] The German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) recently proposed a prognostic model to predict the risk of CNS relapse incorporating the 5 clinical factors (age > 60 years, LDH > normal, stage III or IV, ECOG PS > 1, and involvement of the kidney or adrenal gland), and this model[24] was validated in an independent cohort of 1597 patients by Savage et al.[25] This prognostic model separated patients into 3 risk categories based on the rate of developing CNS disease at 2 years: low-risk (0 or 1 risk factor; rate of CNS disease ≤1%), intermediate-risk (2 or 3 factors; rate of CNS disease 2%–10%) and high-risk group (4 or 5 factors; rate of CNS disease at 17%). In both datasets, involvement of the kidney or adrenal gland was highly associated with CNS relapse. Lumbar puncture should be considered in patients with 4 to 6 risk factors identified in the DSHNHL prognostic model, the presence of 2 or more extranodal sites plus elevated LDH, involvement of testes, HIV-associated lymphoma, or double-hit lymphoma (DHL). The diagnostic yield is improved if flow cytometric analysis of cerebrospinal fluid is performed.

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Treatment

Stage I-II

In the SWOG 8736 study, CHOP (3 cycles) followed by involved field radiation therapy (IFRT) produced significantly better 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;[26] 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.[27] Another randomized trial (ECOG 1484 study) showed that the addition of radiation therapy (RT) to CHOP (8 cycles) prolonged disease-free survival (DFS) in patients with limited stage DLBCL who had experienced complete remission (CR) to CHOP alone (6-year DFS, 73% for IFRT; 56% for observation).[28]

In the a GELA study (LNH 93-4), however, the addition of RT to 4 cycles of CHOP did not provide any advantage over 4 cycles of CHOP alone for the treatment of older patients with low-risk localized aggressive lymphoma. The estimated 5-year event-free survival (EFS) was not different between the 2 groups (61% and 64%, respectively) and the 5-year estimated OS rates were 68% and 72%, respectively.[29] 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, ECOG PS 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%.[30] 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). A phase III trial (MabThera International Trial [MInT]) compared 6 cycles of CHOP-like chemotherapy to 6 cycles of CHOP-like chemotherapy plus rituximab in patients younger than 60 years of age with 0-1 IPI risk factors.[31,32] All 3 quarters of patients had limited stage

disease, and RT was included for all extranodal sites of disease or any site larger than 7.5 cm. The trial found a benefit to rituximab-based 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 with chemotherapy alone.[32] Abbreviated course R-CHOP (3 cycles) with RT is also associated with better upfront disease control and reduced short-term toxicity compared with 6-8 cycles of R-CHOP alone.[33]

Stage III-IV

R-CHOP-21 is the standard treatment for patients with advanced-stage DLBCL based on the results of the GELA study (LNH98-5), which showed that the addition of rituximab to CHOP-21 improved PFS and OS in older patients with advanced DLBCL. In this study, older patients (age 60–80 years; N=399) were randomized to receive 8 cycles of R-CHOP or CHOP.[34-36] 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.[37] These findings have been confirmed in 3 additional randomized trials, including the 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.[31,32] The Dutch HOVON and Nordic Lymphoma Group study (8 cycles of R-CHOP-14 or CHOP-14) and the ECOG/CALGB study confirmed the findings in patients older than 60 years.[38,39] The ECOG/CALGB 9703 study also showed that maintenance rituximab in first CR offered no clinical benefit to patients who received R-CHOP as their induction therapy.[39]

The DSHNHL studies showed that 6 cycles of dose dense CHOP (CHOP-14) as first-line therapy was superior to 6 cycles of CHOP-21, before the introduction of rituximab.[40-42] In the RICOVER 60-trial, older patients (aged 61–80 years) were randomized to receive 6 or 8 cycles CHOP-14 with or without 8 cycles of rituximab.[43,44] RT was administered to sites of initial bulky disease with or without extranodal involvement. The addition of rituximab to 6 or 8 cycles of CHOP-14 (R-CHOP-14) significantly improved clinical outcomes compared with CHOP-14 alone. With a median observation time of 82 months, EFS was significantly improved after R-CHOP-14 (P<.001) compared with CHOP-14. The OS rate was

also significantly improved in patients treated with R-CHOP-14. No difference in clinical benefit but increased toxicity was seen in patients treated with 8 cycles compared with 6 cycles of therapy.[44] 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.

The results of the RICOVER-noRTh trial showed that omission of RT to bulky sites 7.5 cm or larger or extranodal sites is associated with inferior PFS and OS rates in patients with stage III-IV DLBCL.[45] Similarly, subgroup analyses of the MInT and RICOVER-60 trial showed that patients with skeletal involvement significantly benefitted from RT to sites of skeletal involvement.[46] Although retrospective subgroup analyses may be subject to selection biases, the benefit of RT held up on multivariate analysis in both studies and may be considered.

Two randomized trials have compared R-CHOP-21 with dose-dense R-CHOP-14.[47,48] 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.[47] 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 the fact that all patients in the R-CHOP-14 arm received primary growth factor prophylaxis with granulocyte colony-stimulating factor (G-CSF) whereas no primary prophylaxis was given with R-CHOP-21.[47] Notably, no difference in outcome was seen between GCB-like and non-GCB-like DLBCL using 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 older 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 seen in terms of 3-year EFS (56% vs 60%; P=.7614), PFS (60% vs 62%), or OS rates (69% vs 72%).[48] Grade 3 or 4 neutropenia was observed more frequently in the R-CHOP-14 arm (74% compared with 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%).

The results of the dense-R-CHOEP trial showed that doubling the number of rituximab (375 mg/m²) infusions (from 6 to 12) administered with 8 x CHOEP-14 did not result in a significant improvement of EFS and OS in aaIPI-2 patients with DLBCL.[49] There was an improvement in EFS and OS rates in patients with aaIPI-3; however, it was not statistically significant because this group included only 11 patients.

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.

Data from multiple randomized trials have shown that among older adults, women benefited more from the addition of rituximab than men.[50] This could be explained by a slower clearance rate of rituximab in older women. A prospective non-randomized trial that evaluated R-CHOP with rituximab dose of 500 mg/m² in men over the age of 60 with DLBCL demonstrated that the serum levels and OS rates improved compared with historical data in older men treated with a rituximab dose of 375mg/m², similar to older women treated with rituximab dose of 375 mg/m².[51] Based on these data, a rituximab dose of 500 mg/m² may be considered in older men (> 60 years of age but under the age of 80 years) treated with R-CHOP.

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) plus rituximab (DA-EPOCH-R) has shown significant activity in patients with untreated DLBCL.[52,53] In a multicenter phase II CALGB study, DA-EPOCH-R (6–8 cycles) was evaluated in patients with previously untreated DLBCL (n=69; 48 patients with DLBCL).[52] 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 time to progression (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 rates in these subgroups were 95%, 92%, and 43%, respectively (P<.001).[52] The TTP rate was significantly higher in the subgroup with GCB phenotype compared with non-GCB phenotype (100% vs 67%; P=.008); the GC phenotype was also associated with a higher 5-year OS rate (94% vs 68%; P =.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 seen. The most common grade 3 non-hematologic toxicities included neuropathies (25%), fatigue (16%), and arrhythmia (6%).[52] In another multi-institutional study that assessed the safety and efficacy of DA-EPOCH-R in patients with untreated large B-cell lymphomas and poor prognosis (IPI>1; n=81; DLBCL, n=68; primary mediastinal DLBCL, n =6) and follicular lymphoma grade 3b, n=7), DA-EPOCH-R produced a CR rate of 80.2%.[53] After a median follow-up time of 64 months, 10-year EFS and OS rates were 47.8% and 63.6%, respectively.[53]

An ongoing phase III randomized study (CALGB 50303) is evaluating DA-EPOCH-R compared with R-CHOP in patients with untreated DLBCL. Pending results of that study, there is insufficient evidence to recommend DA-EPOCH-R as standard initial therapy for patients with 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, DHL, and primary mediastinal B-cell lymphoma (PMBL).

Patients older than 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 evaluated 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.[54] 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.[55] Grade 3 or higher neutropenia was the most frequent hematologic toxicity seen in 59 patients. The guidelines have included R-miniCHOP as a treatment option for patients older than 80 years.

Role of High-Dose Therapy and Autologous Stem Cell Rescue

In the randomized GELA LNH87-2 study, patients with DLBCL in first CR after induction therapy received consolidation therapy with either sequential chemotherapy or high-dose therapy and autologous stem cell rescue (HDT/ASCR).[56] 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 DFS rate (55% vs 39%; P=.02) and 8-year OS rate (64% vs 49%; P=.04) in the high-intermediate/high-risk subset.[56] This study was performed before rituximab-based induction chemoimmunotherapy.

In the SWOG 9704 trial, 253 patients with high-intermediate/high IPI were randomized to receive R-CHOP (3 cycles) or HDT/ASCR, following initial remission with 5 cycles of CHOP or R-CHOP induction.[57] The 2-year PFS rate was significantly higher with HDT/ASCR compared with chemoimmunotherapy alone (69% vs 55%; P=.005); the 2-year OS rates were not significantly different (74% vs 71%, respectively; P=.30). In an exploratory subset analysis, HDT/ASCR was associated with an OS benefit for patients with high-risk disease. In this subgroup, the 2-year OS rates were 82% and 63% respectively, for patients treated with HDT/ASCR and chemoimmunotherapy. Notably, in this study a third of the patients did not receive rituximab as part of their induction regimen.

The role of upfront HDT/ASCR has also been evaluated in patients with high-risk aggressive lymphomas. In prospective studies, there was no benefit to upfront HDT/ASCR compared with first-line rituximab-based chemoimmunotherapy, except in high-risk IPI patients.[58-60] However, this remains controversial because this finding emerged only on a retrospective subset analysis involving a small number of patients. Presently, first-line consolidation with HDT/ASCR is recommended only in selected patients with high risk (category 2B) or in the context of a clinical trial.

NCCN Recommendations

R-CHOP (3 cycles) with involved site radiation therapy (ISRT) or R-CHOP (6 cycles) with or without ISRT is recommended for patients with non-bulky (<7.5 cm) stage I or II disease.[30,32] Patients with bulky disease (≥7.5 cm) may be treated more effectively with R-CHOP (6 cycles) with or without

locoregional RT (category 1).[32] Regarding the addition of RT, it is important to consider the results from the RICOVER-noRTh trial that showed a significant advantage to adding RT to initial bulky sites 7.5 cm or larger.[45] R-mini-CHOP may be substituted in patients over age 80 to improve chemotherapy tolerability[54,55] and ISRT alone is recommended for patients who are not candidates for any chemotherapy. See "Principles of Radiation Therapy" in the guidelines (available at NCCN.org) for the ISRT dose recommendations.

R-CHOP-21 for a total of 6 cycles (category 1) is recommended for patients with stage III-IV disease.[32,38,39] In selected patients, RT to bulky sites may be beneficial (category 2B). In patients with bulky disease or impaired renal function, initial therapy should include monitoring and prophylaxis for tumor lysis syndrome. R-CHOP-21 for a total of 6 cycles is the preferred regimen due to reduced toxicities. Other comparable anthracycline-based regimens may also be used. Suggested alternate regimens include DA-EPOCH-R (category 2B)[52,53] or dose-dense R-CHOP-14 (category 3).[47,48] Participation in clinical trials is recommended if available.

Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac function should include more frequent cardiac monitoring. See BCEL-B (pages 206–208) for regimens that are used at NCCN Member Institutions for the first-line treatment of DLBCL in very frail patients or those with poor left ventricular function, based on limited published data.

For concurrent presentation of CNS disease with parenchymal involvement, systemic methotrexate (≥ 3 g/m^2) should be incorporated as part of the treatment plan. Intrathecal methotrexate/cytarabine and/or 3 to 3.5 g/m^2 systemic methotrexate should be incorporated as part of the treatment plan for concurrent presentation of CNS disease with leptomeningeal involvement. Ommaya reservoir placement should be considered in patients with leptomeningeal disease. When administering high-dose methotrexate, patients must be pretreated with hydration and alkalinization of the urine, and then receive leucovorin rescue beginning 24 hours after initiation of methotrexate infusion. Renal and hepatic function must be monitored. Adequate recovery of blood counts should be confirmed before starting the next cycle of R CHOP.

Patients with risk factors for CNS involvement (age > 60 years, elevated LDH, stage III or IV, ECOG PS > 1, extranodal sites >1, kidney or adrenal gland involvement) should be considered for CNS prophylaxis.[21–25] The method by which prophylaxis should be given is controversial. Intrathecal methotrexate given at least once per systemic treatment cycle has been used for many years. More recent retrospective studies have suggested that high-dose intravenous methotrexate-based prophylaxis may be associated with a lower incidence of CNS relapses.[61–64] 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.[61] However, other reports suggest that CNS prophylaxis is insufficient to prevent CNS relapse.[65,66] 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.

Response Assessment

Interim restaging is performed to identify patients whose disease has not responded to or has progressed on induction therapy. A negative PET scan after 2 to 4 cycles of induction therapy has been associated with favorable outcomes in several studies.[67–70] In patients with aggressive lymphoma (N=90) treated with first-line anthracycline-based induction chemoimmunotherapy with rituximab (41% of patients), those with a negative PET scan (n=54) after 2 cycles of induction therapy had significantly higher 2-year EFS (82% vs 43%; P<.001) and OS rates (90% vs 61%; P=.006) compared with those with a positive PET scan (n=36).[69] In another study, among 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 those with a negative PET scan (n=77) compared with a positive PET scan (n=22) after 4 cycles of induction therapy (80% vs 36%; P<.0001).[70]

However, interim PET scans 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

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4 cycles of accelerated R-CHOP), only 5 of 37 patients with a positive interim PET scan had a biopsy showing 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.[71] A retrospective analysis of 88 newly diagnosed patients with DLBCL treated with 6 to 8 cycles of R-CHOP also reported only a minor difference in the 2-year PFS rates between patients with a positive interim PET scan and a negative interim PET scan; the 2 year PFS rates were 72% and 85%, respectively (P=.0475).[72] Conversely, the end-of-treatment PET scan was highly predictive of PFS; the 2-year PFS rate was 64% for patients with a final positive PET scan compared with 83% for those with a final negative PET scan (P<.001).

More recent reports have also confirmed the limited prognostic value of interim PET scans in patients with DLBCL treated with R-CHOP.[73–76] In a prospective study that evaluated the predictive value of interm PET scans after 2 cycles of R-CHOP in 138 evaluable patients, the 2-year EFS rate was significantly shorter for patients with a positive interim PET scan than for those with a negative interim PET scan (48% vs 74%; P=.004); however, the 2-year OS was not significantly different between the 2 groups (88% vs 91%; P=.46).[75]

Therefore, interim PET imaging 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 should be strongly considered to confirm PET positivity before additional therapy. If the biopsy is negative, the planned course of treatment as recommended for PET-negative guidelines should be completed. Patients should undergo evaluation before receiving RT, including all positive studies. If RT is not planned, interim restaging after 3 to 4 cycles of R-CHOP is appropriate to confirm response. End of treatment restaging is performed on completion of treatment. The optimal time to end of treatment restaging is not known. However, the panel recommends waiting for 6 to 8 weeks after completion of therapy before repeating PET scans.

Response assessment by PET-CT should be done according to the 5-point scale.[15,77] The 5-point scale is based on the visual assessment of fluorodeoxyglucose (FDG) uptake in the involved sites relative to that of the mediastinum and the liver.[78–80] A score of 1 denotes no abnormal FDG-avidity, while a score of 2 represents uptake less than the mediastinum. A score of 3 denotes uptake greater than the mediastinum but less than the liver, while scores of 4 and 5 denote uptake greater than the liver and greater than the liver with new sites of disease, respectively. Different clinical trials have considered scores of either 1 to 2 or 1 to 3 to be PET-negative, while scores of 4 to 5 are universally considered PET-positive. A score of 4 on an interim or end of treatment restaging scan may be consistent with a partial response if the FDG-avidity has declined from initial staging, while a score of 5 denotes progressive disease.

Follow-up

Considerable debate remains regarding the routine use of imaging for surveillance in patients who experience 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 as well as increased health care 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 had relapse, 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.[81] The investigators therefore concluded that routine surveillance with CT scans had limited value in the detection of early relapse in patients with a CR after 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.[82] 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.[82] 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.[83] 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).[83] Inconclusive PET scans were obtained in 4% of patients (8 of 183), 6 of those had confirmed relapse 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 patients had confirmed relapse based on biopsy evaluation; thus, the positive predictive value of PET/CT scan for detecting relapse was 0.85.[84] In this study, patient age (>60 years) and the presence of clinical signs of relapse were significant predictors of disease relapse.

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.[85–87] 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).[85] Another study reported a positive predictive value of 56% for surveillance PET-CT scans in patients IPI score less than 3 compared with 80% for patients with IPI score of 3 or greater, suggesting that surveillance PET-CT has a very limited role in the majority of patients in CR after primary therapy.[86] A multi-institutional retrospective study evaluated the utility of surveillance scans in 2 independent prospectively enrolled cohorts of patients with DLBCL treated with anthracycline-based chemoimmunotherapy.[87] In one cohort (n=680; 552 patients entered posttreatment observation), posttreatment surveillance scans detected DLBCL relapse before clinical manifestations only in 1.6% of patients (9 of 552 patients) during a planned follow-up visit. In another cohort (n=261; 222 patients entered posttreatment observation), surveillance imaging detected asymptomatic relapse only in 1.8% of patients (4 of 222 patients). A population-based study of patients from the Danish and Swedish lymphoma registries also showed that imaging-based surveillance strategy had no impact on survival for patients DLBCL in first CR.[88]

A multi-institutional retrospective study identified the EFS at 24 months (EFS24) as a prognostic factor for improved OS in patients with DLBCL treated with anthracycline-based chemoimmunotherapy, suggesting that EFS24 would be useful for developing strategies for posttherapy surveillance, patient counseling, and as an end point in clinical studies.[89]

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. PET/CT may be preferable for patients with primarily osseous presentations, with the caveat that bone remodeling may also be FDG-avid, so a biopsy is recommended for PET positive sites before instituting second line therapy.

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

When the treatment plan involves RT, restaging should be done after completion of first-line chemoimmunotherapy prior to initiation of RT, as the dose of RT will be influenced by the result (see "Principles of RT," available in these Guidelines, at NCCN.org). If interim restaging shows CR (PET-negative), the planned course of treatment with same dose of RT is completed. If the interim restaging demonstrates a partial response (PR; PET-positive), treatment with a higher dose of RT is appropriate. It is appropriate to enroll patients with an interim PR on a clinical trial. At the present time, no data are available to suggest that a PR with persistent PET positivity after 3 cycles should prompt a change in

treatment. If the PET scan is positive after 6 cycles of RCHOP, the patient can proceed to second-line therapy followed by HDT/ASCR with or without RT. Primary refractory or progressive disease is managed as refractory or relapsed disease. After end of treatment restaging, follow-up at regular intervals (every 3 to 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 clinically indicated. Patients with PR and those with no response to treatment or progressive disease are treated as described for relapsed or refractory disease. Palliative RT is recommended for selected patients who are not candidates for chemoimmunotherapy.

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

If interim staging (after 2–4 cycles of RCHOP-21) demonstrates a CR and PR, the planned course of RCHOP to a total of 6 cycles is completed. End of treatment restaging is performed on completion of treatment. After end of treatment restaging, 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 patients at high risk (category 2B).[56,57] 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 subsequently for relapsed or refractory disease. Palliative RT is recommended for selected patients who are not candidates for chemoimmunotherapy.

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).[90] 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 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).[90] This study was performed before 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).[91] In this analysis, 25% of patients had received rituximab-based therapy before 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 vs 6 months; P<.001).[91]

The efficacy of second-line therapy is predicted by the second-line age-adjusted IPI.[92,93] Furthermore, pretransplantation PET scans have been identified as predictive factors after HDT/ASCR.[94,95] PET positivity before transplant and chemoresistance are associated with a poor outcome.[96,97] The results of studies from the GEL-TAMO group and ABMTR suggested that HDT/ASCR should be considered for patients who do not experience CR but who are still sensitive to chemotherapy.[98–100]

Rituximab as a single agent is reserved for the frail older patient with relapsed or refractory DLBCL.[101] Several chemotherapy regimens (with or without rituximab) have been evaluated in patients with relapsed or refractory DLBCL.[102–110] In a phase II study, rituximab in combination with ICE (R-ICE) 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%).[107]

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 chemo-sensitive patients.[111,112] 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).[112] Notably, patients with relapse 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 gene rearrangement (with or without concurrent in BCL2 and/or BCL6 gene rearrangements) had poor outcomes regardless of treatment arm.[113] The 4-year PFS was 18% among patients with MYC gene rearrangements compared with 42% in those without (P=.032); 4-year OS was 29% and 62%, respectively (P=.011). Among patients with MYC gene rearrangements, the 4-year PFS was 17% with R-DHAP and 19% with R-ICE; OS was 26% and 31%, respectively.[113] Interestingly, a subgroup analysis from the CORAL study (Bio-CORAL) showed that for patients with a GCB phenotype (based on Hans algorithm), R-DHAP resulted in improved PFS (3-year PFS 52% vs 31% with R-ICE).[114] This difference was not observed among patients with non-GCB phenotype (3-year PFS 32% with R-DHAP vs 27% with R-ICE).[114] R-DHAP and R-ICE are acceptable options for patients with relapsed or refractory DLBCL.

The CORAL study was also designed to evaluate the role of rituximab maintenance (every 2 months for 1 year) after ASCR. Among the patients randomized after 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.[112] 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.[112]

Gemcitabine-based chemotherapy regimens such as GDP (gemcitabine, dexamethasone, cisplatin) and GemOx (gemcitabine and oxaliplatin) in combination with rituximab have also been effective in relapsed or refractory DLBCL.[115–120] Bendamustine in combination with rituximab [121–124] and lenalidomide (with or without rituximab)[125–129] have also been evaluated in patients with relapsed or refractory DLBCL.

In a small dose-escalation study of patients with relapsed/refractory aggressive NHL (N=9; DLBCL, n=5), the combination of bendamustine and rituximab (BR) resulted in PR in 1 patient (90 mg/m² dose of bendamustine; n=3) while the same combination with 120 mg/ m² dose of bendamustine (n=6) resulted in CRs in 5 patients and a PR in 1 patient.[122] In a recent phase II study of patients with relapsed/refractory DLBCL , BR regimen (bendamustine dose 120 mg/m²) resulted in an ORR of 63% (CR in 37% of patients).[123] 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-based regimens.[123] The median PFS was approximately 7 months. The most common grade 3 or 4 toxicities were neutropenia (76%) and thrombocytopenia (22%).[123] In older patients with relapsed/refractory DLBCL (59 patients; median age 74 years; 48 evaluable patients), the BR regimen (with bendamustine dose 120 mg/m²) resulted in an ORR of 45.8% (15.3% CR; 30.5% PR).[124] 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.

Lenalidomide monotherapy has been shown to induce an overall response rate (ORR) of 28% in patients with relapsed or refractory DLBCL.[125,126] In a multicenter randomized study, 102 patients with relapsed/refractory DLBCL (≥2 prior therapies or ineligible for HDT/ASCR; GCB-DLBCL, n=48; non-GCB DLBCL, n=54) were randomized to lenalidomide monotherapy or single-agent investigator's choice.[130] Lenalidomide resulted in improved ORR, PFS, and OS in patients with non–GCB subtype compared with those with GCB subtype. In another phase II trial, 45 patients with relapsed or refractory DLBCL (n=32), transformed large cell lymphoma (n=9) or follicular lymphoma grade 3 (n=4), lenalidomide in combination with rituximab induced ORR in 33% of patients.[128] The median response duration, PFS, and OS were 10.2 months, 3.7 months, and 10.7 months, respectively.[128] Myelosuppression was the most common grade 3 or 4 toxicity.

Brentuximab vedotin, a CD30-directed antibody-drug conjugate, has demonstrated activity in patients with relapsed or refractory CD30-positive lymphomas. A phase 2, open-label study evaluated the efficacy of brentuximab vedotin in relapsed or refractory CD30-positive NHL.[131] In a planned subset analysis that included 49 patients with DLBCL, the

ORR was 44% (17% CR) with a median duration of 16.6 months. Although no statistical correlation was seen between the response and the level of CD30 expression, all patients with responding disease had quantifiable CD30 by IHC.

Brentuximab vedotin (for CD30-positive DLB-CL), lenalidomide with or without rituximab (for non-GCB-DLBCL) and a bendamustine with or without rituximab are included as options for patients with relapsed or refractory DLBCL who are not candidates for HDT/ASCR.

NCCN Recommendations

All patients with relapsed or refractory DLBCL should be considered for enrollment in available clinical trials. HDT/ASCR is the treatment of choice for patients with relapsed or refractory DLBCL that is chemosensitive at relapse. Patients who are candidates for HDT/ASCR should be treated with second-line chemotherapy, with or without rituximab (depending on whether the disease is deemed to be refractory to prior rituximab regimens). See BCEL-B (pages 206–208) for suggested regimens for relapsed or refractory disease.

Patients with CR or PR to second-line therapy should be considered for further consolidation with HDT/ASCR (category 1 for patients with CR) with or without RT.[90,91] ISRT before HDT/ASCR has been shown to result in good local disease control and improved outcome.[132] Additional RT can be given to limited sites with prior positive disease before or after ASCR. 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 or other chemotherapy regimens (with or without rituximab) as listed on BCEL-B (see pages 206–208).

Patients with disease relapse after HDT/ASCR should be treated in the context of a clinical trial, or treatment should be individualized. However, those with progressive disease after 3 successive regimens are unlikely to derive additional benefit from currently available chemotherapy regimens, except for patients who have experienced a long disease-free interval.

PMLBL

PMBL is a distinct subtype of NHL that can be histologically indistinguishable from DLBCL and that tends to occur in young adults with a median age of 35 years with a slight female predominance.[133,134] PMBL arises from thymic B-cells with initial local regional spread to supraclavicular, cervical, hilar nodes and into the mediastinum and lung.[133] Widespread extranodal disease is uncommon at initial diagnosis, present in approximately one quarter of patients, but can be more common at recurrence.[134] Clinical symptoms related to rapid growth of a mediastinal mass include superior vena cava syndrome, pericardial and pleural effusions.

GEP has indicated that PMBL is distinct from DLBCL; the pattern of gene expression in PMBL is more similar to classic Hodgkin lymphoma (cHL).[135,136] 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.[134] CD10 positivity is seen in 8% to 32% of 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.[134] Age-adjusted IPI is of limited value in determining the prognosis of PMBL at diagnosis.[133,137,138] In a retrospective analysis of 141 patients from Memorial Sloan Kettering Cancer Center, 2 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.[137]

In retrospective analyses, intensive chemotherapy regimens have appeared more effective than CHOP[138–140] and the addition of IFRT has been associated with improved PFS; however, these studies were conducted in the pre-rituximab era.[141,142] The results of subsequent retrospective studies suggest that although the addition of rituximab to MACOP-B (methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) or VACOP-B

(etoposide, leucovorin, doxorubicin, cyclophospha-mide, vincristine, prednisone, and bleomycin) did not appear to result in significant differences in clinical outcomes, its addition to CHOP improves outcome in patients with PMBL.[143–147] In an analysis of the sub-group of patients with PMBL (N=87) from the ran-domized 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).[144] The MInT study, however, only included young low-risk patients with IPI scores 0 to 1. In a recent follow-up report with a median observa-tion time of 62 months in patients with PMBL, the in-crease in EFS with rituximab remained significant at 5 years (79% vs 47%; P=.011).[146] The 5-year PFS was also significantly increased in the rituximab arm (90% vs 60%; P=.006); 5-year OS was not significantly dif-ferent (90% vs 78%), but was similar to OS outcomes in patients with DLBCL in this study (92% with ritux-imab vs 81% without; P<.001).[146] In a retrospective analysis of 95 consecutive patients treated with che-motherapy (VACOP-B or CHOP) with and without rituximab, the 5-year PFS and OS rates were 79% and 97% for patients treated with rituximab-based chemo-therapy compared with 58% and 88%, respectively, for those treated with chemotherapy alone. The 5-year PFS rates in patients treated with R-VACOP-B, R-CHOP, VACOP-B, and CHOP were 83%, 69%, 62%, and 20%, respectively,[148] with 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.[148] At a median follow-up for surviving patients at 3 years, the OS and PFS rates were 88% and 78%, respectively[148] with a sequential dose-dense RCHOP followed by ICE con-solidation (Memorial Sloan Kettering Cancer Center protocol 01-142). A retrospective analysis of 63 pa-tients with PMBL treated with R-CHOP found a 21% rate of primary induction failure, with adverse predic-tors of outcome being advanced stage and high-risk IPI scores, suggesting that R-CHOP may not be the optimal chemotherapy backbone in PMBL, particu-larly for high-risk patients.[149]

DA-EPOCH-R has also been evaluated in small cohorts of patients with PMBL.[150,151] A small pro-spective NCI study of the DA-EPOCH-R without RT demonstrated an encouraging 91% EFS at a me-dian follow-up of 4 years. In a subsequent prospec-tive phase II study from the NCI, DA-EPOCH-R (6–8 cycles) and filgrastim, without RT, was evaluat-ed in 51 patients with previously untreated PMBL.[150] Stage IV disease was present in 29% of patients. After treatment with DA-EPOCH-R, 2 patients showed persistent focal disease and 1 patient had dis-ease progression; 2 of these patients required medias-tinal 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. Hospital-ization for febrile neutropenia occurred in 13% of cycles.[150] 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. A single institution retrospective analysis also showed that R-CHOP/R-VACOP-B with RT and DA-EPOCH-R without RT result in excellent outcomes in patients with stage I or II PMBL.[151]

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 (with or without) RT are included as options for first-line therapy.

- R-CHOP
- DA-EPOCH-R150
- R-CHOP followed by ICE[148] (category 2B)

Posttreatment PET-CT is considered essential; if PET-CT is negative at the end of treatment and ini-tial disease was nonbulky, patients may be observed. Residual mediastinal masses are common. The role of consolidation RT remains unclear. A few studies have evaluated the utility of PET scans (based on the 5-PS) to identify patients at high-risk of progression who could be considered for RT after completion of chemotherapy.[152,153] However, these findings need to be confirmed in larger prospective randomized trials. For patients initially treated with R-CHOP, consolida-tion with RT should be considered, particularly if in-creased FDG-activity persists in the primary tumor. For patients who are PET-CT negative after more inten-sive therapies (eg, DA-EPOCH-R), observation may be appropriate. If PET-CT is positive, biopsy is recom-mended before additional treatment is contemplated.

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Grey Zone Lymphoma

Grey zone lymphomas, a provisional diagnostic category included in the 2008 WHO classification, refer to a group of lymphomas with features intermediate between DLBCL and cHL.[146,154–157] Other synonyms include large B-cell lymphoma with Hodgkin features or Hodgkin-like anaplastic large cell lymphoma. 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.[156] Necrosis without neutrophilic infiltration is frequently present.[146,154,156] Patients with gray zone lymphomas may present with mediastinal or nonmediastinal disease. Mediastinal grey zone lymphomas are more commonly seen in young adult men between the ages of 20 to 40 years and are characterized by the presence of a large anterior mediastinal mass with or without supraclavicular lymph node involvement.[154,155,157] Nonmediastinal gray zone lymphomas occur in older patients, have a higher incidence of bone marrow involvement, more than one extranodal disease, advanced stage disease, and high-risk IPI score than mediastinal grey zone lymphomas.[158] In a retrospective multicenter analysis of 112 patients with grey zone lymphomas, mediastinal presentations were found in 43% of patients, while 57% presented with nonmediastinal grey zone lymphomas.[158]

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.[154,156,159] BCL6 is variably expressed. EBV is more often negative.[154,155] If the morphology more closely resembles PMBL, absence of CD20, or CD15 positivity, 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.[154] 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 of CpG targets between PMBL and cHL.[160] 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, 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.[160]

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.[156,159,161] In a prospective study that evaluated 6 to 8 cycles of DA-EPOCH-R in a small group of patients with mediastinal grey zone lymphoma (n=24), the EFS and OS were 62% and 74%, respectively, at the median follow-up of 59 months.[162] With a median follow-up of 5 years, the EFS (62% vs 93%; P=.0005) and OS (74% vs 97%; P=.0012), were significantly lower for patients with mediastinal grey zone lymphoma compared with patients with PMBL (n=51) enrolled in the same study. In a multicenter retrospective analysis of gray zone lymphoma (that did not have central pathology review), patients treated with CHOP-like regimens with or without rituximab had superior outcomes compared to subjects treated with ABVD, with 2 year PFS rates of 52% and 22%, respectively.[158]

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. 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. The addition of rituximab is generally suggested for tumors expressing CD20. In the absence of suitable clinical trials, R-CHOP-21 or DA-EPOCH-R should be considered. 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.

DHL

DLBCL or high-grade B-cell lymphoma unclassifiable (intermediate between DLBCL and BL) with *MYC* gene rearrangement in addition to *BCL2* and/or *BCL6* gene rearrangements by FISH or standard cytogenetics are known as DHL. Immunohistochemical staining can also identify DLBCL with dual expression of both MYC and BCL2 proteins, known as "double-expressing" DLBCL (DEL).[163,164] These patients have an inferior prognosis compared with those with DLBCL as a whole, but not to the same magnitude as patients with true DHL on the basis of gene rearrangements. FISH testing for *MYC*, *BCL2*, and *BCL6* gene rearrangements is recommended for those with expression of MYC and either BCL2 or BCL6 by IHC, and a GCB-like immunophenotype.

DHL have been seen in 2% to 11% of newly diagnosed patients with DLBCL. Nearly all DHL are GCB-DLBCL and are characterized by highly aggressive clinical behavior and overlapping pathologic features with DLBCL, Burkitt lymphoma and B-cell lymphoblastic lymphoma/leukemia (B-LBL).[165] DHL are highly aggressive with very poor clinical outcomes, even with rituximab-based chemoimmunotherapy or intensive therapy with stem cell transplantation.[163,164,166,167]

In a series of 193 patients with DLBCL uniformly treated with standard R-CHOP, the median OS (13 vs 95 months) and PFS (6 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 DHL compared with those without DHL.[163] In another study with a longer follow-up, 5-year PFS and OS were 18% and 27%, respectively, in patients with DHL treated with R-CHOP.[164] 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.[163,164] 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.[163,164]

Data from retrospective studies suggest that more intensive chemotherapy regimens may result in better outcomes.[168–170] In a multicenter retrospective analysis of 106 patients (77% of patients had DHL characterized by *MYC* and *BCL2* gene rearrangements), treatment with intensive regimens such as DA-EPOCH-R, R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone) or R-CODOX-M/IVAC (rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high dose cytarabine) resulted in superior CR and PFS compared R-CHOP.[168] A recent meta-analysis compared survival outcomes in patients with DHL treated with more aggressive regimens including R-HyperCVAD, R-CODOX-M/IVAC or R-EPOCH versus standard-dose regimens (R-CHOP) in the first-line setting.[171] The median PFS for the R-CHOP, DA-EPOCH-R and other dose intensive regimens was 12.1, 22.2, and 18.9 months, respectively. DA-EPOCH-R significantly reduced the risk of progression compared with R-CHOP; however, OS was not significantly different across treatment approaches.

DA-EPOCH-R is being evaluated in a prospective phase II study of 52 patients with newly diagnosed with DLBCL or B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL).[172] All patients had a MYC gene rearrangement. *BCL2* gene rearrangement and BCL2 overexpression were identified in 45% and 56% of patients respectively. Preliminary reports from this study showed that PFS and OS were 79% and 77%, respectively, for all patients, at a median follow-up of 14 months. PFS was 87% and 64% in cases that were FISH positive (double-hit) and IHC positive for BCL2, respectively.[172] Additional prospective studies are needed to evaluate the efficacy of DA-EPOCH-R as well as other regimens and stem cell transplantation strategies in patients with DHL. Alternative treatment strategies are needed to improve outcomes in this poor-risk patient population.

The standard of care for the treatment of patients with DHL or DEL has not been established. R-CHOP is associated with inferior outcomes. DA-EPOCH-R, R-HyperCVAD (alternating with high-dose methotrexate and cytarabine) or R-CODOX-M/R-IVAC are used in NCCN Member Institutions for the treatment of DHL. HDT/ASCR is also done at some NCCN Member Institutions; however its role is not established. Currently, no data supports the use of one regimen over another in the setting of DEL, and clinical trials are needed.

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Individual Disclosures of the NCCN Non-Hodgkin's Lymphomas Panel (cont.)				
Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Richard T. Hoppe, MD	None	Davis X-Ray Technology, Inc	None	1/12/16
Steven M. Horwitz, MD	ADC Therapeutics; Celgene Corporation; Infinity Pharmaceuticals; Kyowa Hakko Kirin Co., Ltd.; Millennium Pharmaceuticals, Inc.; Onyx Pharmaceuticals, Inc.; Seattle Genetics, Inc.; and Spectrum Pharmaceuticals, Inc.	ADC Therapeutics; Celgene Corporation; HUYA Bioscience International; ImmunoGen, Inc.; Kyowa Hakko Kirin Co., Ltd.; Millennium Pharmaceuticals, Inc.; Seattle Genetics, Inc.; and Spectrum Pharmaceuticals, Inc.	None	11/17/15
Mark S. Kaminski, MD	Jannsen Pharmaceutica Products, LP	Nordic Nanovector	None	10/21/15
Christopher R. Kelsey, MD	Varian Medical Systems, Inc.	None	None	11/17/15
Youn H. Kim, MD	Eisai Inc.; Innate Pharma S.A.; Kyowa Hakko Kirin Co., Ltd.; Millennium Pharmaceuticals, Inc.; Neumedicines Inc.; Soligenix, Inc.; and TetraLogic Pharmaceuticals Corporation	Actelion Pharmaceuticals Ltd.; Celgene Corporation; Eisai Inc.; Galderma S.A.; Kyowa Hakko Kirin Co., Ltd.; Millennium Pharmaceuticals, Inc.; miRagen Therapeutics; and Seattle Genetics, Inc.	None	1/19/16
Susan Krivacic, MPAff	None	None	None	11/17/15
Ann S. LaCasce, MD	Idera Pharmaceuticals, Inc.; and Seattle Genetics	None	None	11/22/15
Matthew Lunning, DO	None	Celgene Corporation; Gilead Sciences, Inc.; Juno Therapeutics, Inc.; TG Therapeutics, Inc.; Spectrum Pharmaceuticals, Inc.; Genentech, Inc.; Bristol-Myers Squibb Company; and Pharmacyclics	None	12/7/15
Auayporn Nademanee, MD	Jannsen Pharmaceutica Products, LP; and Seattle Genetics, Inc.	Gilead Sciences, Inc.	None	6/26/15
Pierluigi Porcu, MD	Celgene Corporation; Infinity Pharmaceuticals; Innate Pharma; Kyowa Hakko Kirin Co., Ltd.; miRagen Therapeutics; Seattle Genetics, Inc.; and Shape Pharmaceuticals	Kyowa Hakko Kirin Co., Ltd.	Actelion	12/18/15
Oliver Press MD, PhD[a]	Genentech, Inc.; and Roche Laboratories, Inc.	Adaptive Biotechnologies	None	1/20/16
Rachel Rabinovitch, MD	RTOG Data Safety and Monitoring Board	None	None	10/21/15
Nishitha Reddy, MD	Celgene Corporation	Celgene Corporation; and Seattle Genetics, Inc.	Abbott Laboratories; and Gilead Sciences, Inc.	11/17/15
Erin Reid, MD	AbbVie Inc.; AIDS Malignancy Consortium; Bristol-Myers Squibb Company; CALGB/CTSU; Isis Pharmaceuticals, Inc.; Jannsen Pharmaceutica Products, LP; Millennium Pharmaceuticals, Inc.; Pharmacyclics, Inc.; and Takeda Pharmaceuticals North America, Inc.	None	None	1/19/16
Kenneth Roberts, MD	None	Elekta; and IBA	None	12/19/15
Ayman A. Saad, MD	Miltenyi Biotec	ICARE; and IMS Consulting Group	None	1/07/16
Lubomir Sokol, MD, PhD	None	Alexion Pharmaceuticals, Inc.; Celgene Corporation; and Spectrum Pharmaceuticals, Inc.	Jannsen Pharmaceutica Products, LP; and Onyx Pharmaceuticals, Inc.	12/18/15
Lode J. Swinnen, MB, ChB	Abbott Laboratories; and Johns Hopkins University	None	None	11/30/15
Julie M. Vose, MD, MBA	Acerta Pharma; Amgen Inc.; Bristol-Myers Squibb Company; Celgene Corporation; Genentech, Inc.; GlaxoSmithKline; Incyte Corporation; Jannsen Pharmaceutica Products, LP; Kite Pharma, Inc.; Pharmacyclics, Inc.; Seattle Genetics, Inc.; and Spectrum Pharmaceuticals, Inc.	None	None	1/17/16
William G. Wierda, MD, PhD	AbbVie Inc.; Acerta Pharma; Emergent BioSolutions Inc.; Genentech, Inc.; Gilead Sciences, Inc.; GlaxoSmithKline; Jannsen Pharmaceutica Products, LP; Juno Therapeutics, Inc.; Karyopharm Therapeutics; Kite Pharma, Inc.; Novartis Pharmaceuticals Corporation; and Pharmacyclics, Inc.	AbbVie Inc.; Celgene Corporation; Emergent BioSolutions Inc.; Genentech, Inc.; Genzyme Corporation; Gilead Sciences, Inc.; GlaxoSmithKline; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pharmacyclics, Inc.; Roche Laboratories, Inc.; and sanofi-aventis U.S.	None	1/21/16
Joachim Yahalom, MD	None	None	None	9/29/15
Nadeem Zafar, MD	None	None	None	1/13/16
Andrew D. Zelenetz, MD, PhD	AbbVie Inc.; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Genentech, Inc.; and Gilead Sciences, Inc.	Acerta Pharma; Adaptive Biotechnology; Amgen Inc.; Celgene Corporation; Genentech, Inc.; Gilead Sciences, Inc.; Hospira, Inc.; Pharmacyclics, Inc.; and Roche Laboratories, Inc.	None	11/23/15

[a]The following individuals have disclosed that they have a Spouse/Domestic Partner/Dependent Potential Conflict:
 Babis Andreadis MD, MSCE: Genentech, Inc.; and Roche Laboratories, Inc.
The following individuals have disclosed that they have an Employment/ Governing Board, Patent, Equity, or Royalty:
 Oliver Press, MD, PhD: Emergent BioSolutions Inc.