**NON-HODGKIN LYMPHOMA TREATMENT REGIMENS: Diffuse Large B-cell Lymphoma (Part 1 of 5)**

**Clinical Trials:** The National Comprehensive Cancer Network recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced health care team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are provided only to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data become available. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Systemic Therapy for Diffuse Large B-cell Lymphoma

**Note:** All recommendations are Category 2A unless otherwise indicated.

### First-line Therapy

<table>
<thead>
<tr>
<th>REGIMEN</th>
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<tbody>
<tr>
<td><strong>R-CHOP (Category 1)</strong></td>
<td>Days 1, 22, and 43: Rituximab 375mg/m² IV 7 days prior to beginning</td>
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<tr>
<td></td>
<td>CHOP regimen</td>
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<tr>
<td></td>
<td>Day 1: Cyclophosphamide 750mg/m² IV + doxorubicin 50mg/m² IV bolus +</td>
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<td>vincristine 1.4mg/m² IV bolus (max dose 2mg)</td>
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<td></td>
<td>Days 3, 24, and 45: Prednisone 100mg orally 5 days. Repeat cycle 3</td>
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<td></td>
<td>weeks for 3 cycles. Radiotherapy begins 3 weeks after last cycle of</td>
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<tr>
<td></td>
<td>R-CHOP.</td>
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<tr>
<td><strong>Dose-dense R-CHOP 14</strong></td>
<td>Day 1: Cyclophosphamide 750mg/m² IV + doxorubicin 50mg/m² IV +</td>
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<tr>
<td>(Category 3)</td>
<td>vincristine 2mg IV</td>
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<td></td>
<td>Days 1-5: Prednisone 100mg orally. Repeat every 2 weeks for 6 cycles.</td>
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<td></td>
<td>Granulocyte colony-stimulating factor (G-CSF) was given on day 4 or 6.</td>
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<tr>
<td><strong>Dose-adjusted EPOCH +</strong></td>
<td>Day 1: Rituximab 375mg/m² IV</td>
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<tr>
<td>rituximab</td>
<td>Days 1-4: Etoposide 50mg/m² IV + doxorubicin 10mg/m² IV + vincristine</td>
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<td>0.4mg/m² IV</td>
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<td>Day 5: Cyclophosphamide 750mg/m² IV</td>
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<tr>
<td><strong>First-line Therapy for</strong></td>
<td>Days 1-5: Prednisone 60mg/m² orally twice daily. Administer G-CSF 5</td>
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<tr>
<td>Patients With Poor Left</td>
<td>5mcg/kg SQ daily until an ANC &gt;5 × 10⁹/L above nadir level starting</td>
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<tr>
<td>Ventricular Function**</td>
<td>day 6. Repeat cycle every 3 weeks for 6 cycles.</td>
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<tr>
<td><strong>RCEPP</strong></td>
<td>Day 1: Cyclophosphamide 750mg/m² IV + liposomal doxorubicin 30mg/m² IV</td>
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<td></td>
<td>+ vincristine 2mg IV</td>
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<td></td>
<td>Days 1-5: Prednisone 60mg/m² IV</td>
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<td></td>
<td>Day 8: Rituximab 375mg/m² IV for cycle 1; administer on day 0 in</td>
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<td></td>
<td>subsequent cycles. Repeat cycle every 3 weeks for 6-8 cycles.</td>
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<tr>
<td><strong>RCDOP</strong></td>
<td>Day 1: Rituximab 375mg/m² IV + cyclophosphamide 750mg/m² IV +</td>
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<tr>
<td></td>
<td>vincristine 1.4mg/m² (maximum dose 2mg) IV</td>
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<td></td>
<td>Days 1 and 8: Gemcitabine 750-1000mg/m² IV</td>
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<td>Days 1-5: Predisnilone 100mg orally per day.</td>
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<td>Day 9: Pegfilgrastim 6mg SC. Repeat every 3 weeks for 6 cycles (</td>
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<td>Patients considered high risk for CNS relapse can receive methotrexate</td>
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<td>12.5mg IT for 3 cycles).</td>
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<tr>
<td><strong>DA-EPOCH +</strong></td>
<td>Day 1: Rituximab 275mg/m²</td>
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<tr>
<td>rituximab</td>
<td>Days 1-4: Doxorubicin 10mg/m² IV + etoposide 50mg/m² IV + vincristine</td>
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<tr>
<td></td>
<td>0.4mg/m² IV</td>
</tr>
<tr>
<td><strong>RCEOP</strong></td>
<td>Day 5: CHOP regimen</td>
</tr>
<tr>
<td></td>
<td>Days 1-5: Prednisone 60mg/m² IV orally</td>
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<tr>
<td></td>
<td>Day 8: Rituximab 375mg/m² IV</td>
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<tr>
<td></td>
<td>For limited-stage disease, repeat cycle every 3 weeks for 3–4 cycles;</td>
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<td>for advanced-stage disease, repeat cycle every 3 weeks for 6 cycles.</td>
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continued
Systemic Therapy for Diffuse Large B-cell Lymphoma (Part 2 of 5)

First-Line Therapy for Very Frail Patients and Patients >80 Years of Age With Comorbidities

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>DOSING</th>
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| **R-mini-CHOP**<sup>20</sup> | **Day 1:** Rituximab 375mg/m² IV  
**Day 1:** Cyclophosphamide 400mg/m² IV + doxorubicin 25mg/m² IV + vincristine 1mg IV  
**Days 1–5:** Prednisone 40mg/m² orally.  
Repeat every 3 weeks for 6 cycles. |

| **RGCVP**<sup>17</sup> | **Day 1:** Rituximab 375mg/m² IV + cyclophosphamide 750mg/m² IV + vincristine 1.4mg/m² (maximum dose 2mg) IV  
**Days 1 and 8:** Gemcitabine 750-1000mg/m² IV  
**Days 1-5:** Prednisolone 100mg orally per day.  
**Day 9:** Pegfilgrastim 6mg SC.  
Repeat every 3 weeks for 6 cycles (Patients considered high risk for CNS relapse can receive methotrexate 12.5mg IT for 3 cycles). |

| **RCEPP**<sup>14</sup> | **Days 1 and 8:** Cyclophosphamide 600mg/m² IV  
**Day 1:** Etoposide IV 70mg/m² IV (or days 1–3 if not giving oral etoposide)  
**Days 2 and 3:** Etoposide 140 mg/m² orally (rounded to the nearest 50mg capsule)  
**Days 1–10:** Procarbazine 60mg/m² orally + prednisone 60mg/m² orally.  
Repeat every 4 weeks until disease progression, or unacceptable toxicity. |

| **RCDOP**<sup>15,16</sup> | **Day 1:** Cyclophosphamide 750mg/m² IV + liposomal doxorubicin 30mg/m² IV + vincristine 2mg IV  
**Days 1-5:** Prednisone 60mg/m² IV  
**Day 8:** Rituximab 375mg/m² IV for cycle 1; administer on day 0 in subsequent cycles.  
Repeat cycle every 3 weeks for 6–8 cycles. |

**First-line Consolidation (optional)**

| High-dose therapy with autologous stem cell rescue in patients with age-adjusted IPI high-risk disease (Category 2B)<sup>21</sup> | Induced with 5 cycles of CHOP or R-CHOP followed by autotransplantation at the first response to induction therapy with CHOP with or without rituximab for 3 cycles. |

| **Lenalidomide maintenance for patients 60 - 80 years of age (Category 2B)<sup>22</sup>** | **Days 1 to 21:** Lenalidomide 25mg daily.  
Repeat every 4 weeks for 24 months. |

**Concurrent Presentation With CNS Disease**

| Parenchymal<sup>1</sup> | Systemic methotrexate 3g/m² or more on day 15 of a 21-day R-CHOP cycle that has been supported by growth factors. |

| Leptomeningeal<sup>1</sup> | Methotrexate/cytarabine IT. Consider Ommaya reservoir placement and/or systemic methotrexate 3–3.5g/m². |

**Second-line and Subsequent Therapy (for patients with intention to proceed to high-dose therapy)<sup>1,c,d</sup>**

| **DHAP ± rituximab**<sup>23–25</sup> | **Days 1–4:** Cisplatin 100mg/m² IV via 24-hour infusion + cytosine 2g/m² in 2 pulses each given 12 hours apart IV + dexamethasone 40mg orally or IV ± rituximab 375mg/m² IV prior to DHAP.  
Repeat in 3–4 weeks for 6-10 cycles. |

| **ESHAP ± rituximab**<sup>26,27</sup> | **Days 1–4:** Etoposide 40–60mg/m²  
**Days 1–5:** Methyprednisolone 250-500mg IV  
**Day 5:** Cytarabine 2g/m² IV over 2–3 hours  
**Days 1–4:** Cisplatin 25mg/m² IV via 24-hour infusion, ±  
**Day 1 or 5:** Rituximab 375mg/m² IV.  
Repeat every 3–4 weeks for 3 cycles. |

| **GDP ± rituximab**<sup>28,29</sup> | **Days 1 and 8:** Gemcitabine 1000mg/m² IV over 30 minutes  
**Days 1–4:** Dexamethasone 40mg orally  
**Day 1:** Cisplatin 75mg/m² IV OR carboplatin at AUC 5mg·min/mL IV over 30 minutes, ±  
**Day 8:** Rituximab 375mg/m² slow IV infusion for CD20-positive disease.  
Repeat every 3 weeks for up to 6 cycles. |

| **GemOX ± rituximab**<sup>30</sup> | **Day 1:** Gemcitabine 1000mg/m² and oxaliplatin 100mg/m² ± rituximab 375mg/m² IV:  
Repeat every 15 days if ANC >1 × 10⁹/L and platelet count >100 × 10⁹/L; if not, then every 3 weeks. |

| **ICE ± rituximab**<sup>31–33</sup> | **Days 1–3:** Etoposide 100mg/m² IV bolus  
**Day 2:** Carboplatin AUC 5mg·min/mL (max dose 800mg) IV bolus and ifosfamide admixed with mesna both at a dose of 5g/m² via 24-hour continuous IV beginning day 2  
**Days 5–12 (or days 7–14):** Filgrastim 5mcg/kg/day for cycles 1–2, increased to 10mcg/kg/day following cycle 3 until completion of peripheral blood stem cell collection, ±  
**Days 1 and 3:** Rituximab 375mg/m² IV and on cycle 1, give additional dose rituximab 375mg/m² on Day 2.  
Repeat every 14 days or when ANC >1000 cells/ml and platelet count >50000/mL. |
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| MINE ± rituximab<sup>1,3,5</sup> | Day 1: Mitoxantrone 8mg/m² IV  
Days 1-3: ifosfamide 2g/m² IV + mesna IV + etoposide 100mg/m² IV, ±  
Day 1: Rituximab 375mg/m² IV.  
Repeat cycle every 4 weeks for 2 cycles, followed by high-dose chemotherapy and autologous stem cell transplantation (HDC-ASCT). Patients in remission after HDC-ASCT may receive rituximab 375mg/m² IV weekly for 4 weeks. |
| Bendamustine ± rituximab<sup>26,38</sup> | Days 1-2: Bendamustine 120mg/m² IV, ±  
Day 1: Rituximab 375mg/m² IV.  
Repeat every 4 weeks for up to 6 cycles. |
| Brentuximab vedotin for CD30+ disease (Category 2B)<sup>39</sup> | Brentuximab vedotin 1.8mg/kg IV over 30 minutes every 3 weeks.  
Repeat cycle until a maximum of 16 cycles, disease progression, or unacceptable toxicity. |
| CEPP ± rituximab (PO and IV)<sup>40</sup> | Days 1 and 8: Cyclophosphamide 600mg/m² IV  
Day 1: Etoposide IV 70mg/m² IV (or on days 1-3 if not giving oral etoposide)  
Days 2 and 3: Etoposide 140mg/m² orally (rounded to the nearest 50 mg capsule)  
Days 1-10: Procarbazine 60mg/m² orally + prednisone 60mg/m² orally, ±  
Day 1: Rituximab 375mg/m² IV.  
Repeat every 4 weeks until disease progression or unacceptable toxicity. |
| CEP ± rituximab<sup>41</sup> | Day 1: Cyclophosphamide 750mg/m² IV, vincristine 1.4mg/m² IV, and epirubicin 60mg/m² IV  
Days 1-5: Prednisone 100mg/day orally, ±  
Day 0: Rituximab 375mg/m² IV.  
Repeat every 3 weeks for at least 6 cycles. |
| DA-EPOCH ± rituximab<sup>42,43</sup> | Days 2-4: Doxorubicin 15mg/m² via continuous IV infusion + etoposide 65mg/m² via continuous IV infusion + vincristine 0.5mg via continuous IV infusion  
Day 5: Cyclophosphamide 750mg/m² IV  
Day 1-14: Prednisone 60mg/m² orally, ±  
Day 1: Rituximab 375mg/m² IV.  
Repeat every 3 weeks for 4-6 cycles. |
| GDP ± rituximab<sup>39,29</sup> | Days 1 and 8: Gemcitabine 1000mg/m² IV  
Days 1-4: Dexamethasone 40mg IV  
Days 1-3: Cisplatin 25mg/m² IV OR carboplatin AUC 5mg·min/mL on day 1, ±  
Day 1: Rituximab 375mg/m² IV.  
Repeat every 3 weeks for 2-6 cycles (max of 4 cycles if using carboplatin). |
| GemOx ± rituximab<sup>44,45</sup> | Days 1 and 8: Gemcitabine 1200mg/m² 30-minute IV infusion  
Day 2: Oxaliplatin 120mg/m² 2-hour IV infusion, ±  
Day 1: Rituximab 375mg/m² IV.  
Repeat every 3 weeks for 6 cycles. |
| Lenalidomide ± rituximab (non-GCB DLBCL)<sup>46,47</sup> | Days 1-21: Lenalidomide 20mg orally ± rituximab 375mg/m² IV weekly during cycle 1.  
Repeat every 4 weeks until complete response. |
| Rituximab<sup>49</sup> | Day 1: Rituximab 375mg/m² IV during each cycle of chemotherapy for up to 8 infusions. |
| Gemicitabine + vinorelbine ± rituximab (Category 3)<sup>50,51</sup> | Days 1 and 8: Gemcitabine 1000mg/m² + vinorelbine 30mg/m²  
OR  
Days 1 and 8: Gemcitabine 880mg/m² + vinorelbine 25mg/m² + rituximab 375mg/m².  
Repeat every 3 weeks for up to 6 cycles. |
| Ibrutinib (non-GCB DLBCL)<sup>52</sup> | Ibrutinib 560mg orally daily.  
Repeat every 4 weeks until disease progression or unacceptable toxicity. |

* Inclusion of any anthracycline or anthraacenedione in patients with impaired cardiac functioning should have more frequent cardiac monitoring.  
* 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.  
* If additional anthracycline is administered after a full course of therapy, careful cardiac monitoring is essential. Dexrazoxane may be added as a cardioprotectant.  
* Rituximab should be included in second-line therapy if there is a relapse after a reasonable remission (>6 mo); however, rituximab should often be omitted in patients with primary refractory disease.

References


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