Updates (minor changes):

- Separate policy for CNS lymphoma
- High-dose methotrexate prophylaxis for patients at high-risk of CNS recurrence
- GDP now first-line salvage off study
- Use of H. Pylori eradication in gastric DLBCL

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of lymphoma in the WHO classification, accounting for 31% of all lymphomas [1]. This entity consists of cases that would have been classified as diffuse large cell lymphoma (Subtype G) and immunoblastic lymphoma (Subtype H) in the working formulation [2]. The terms, intermediate grade and DLBCL are not completely synonymous however, as intermediate grade in the working formulation includes lymphomas of T-cell origin as well as diffuse small cleaved cell lymphoma (Subtype E).

Diagnosis

The diagnosis of DLBCL is dependent on an adequate biopsy specimen (preferable open surgical biopsy) with immunohistochemistry. Diffuse large B-cell lymphomas are composed of large cells (at least twice the size of small lymphocytes), which mark for B-cell markers such as CD19 and 20. The entity should be distinguished from peripheral T-cell lymphoma, anaplastic large cell lymphoma (CD30 positive) and primary mediastinal B-cell lymphoma with sclerosis [2].

Baseline Investigations

The following investigations are indicated for most patients with DLBCL:

- CBC, differential, blood film
- Serum electrolytes and creatinine
- Liver function tests
- Serum LDH
- Serum uric acid
- HIV serology, Hepatitis BS AG, Hepatitis C antibody
- CT chest, abdomen, pelvis
- Unilateral bone marrow biopsy
- Total body gallium scan
- MUGA scan or 2D echo (see page 2)

Patients who will be managed with palliative intent may have more limited staging investigations with a focus on identification of disease that is likely to require symptomatic management.

CSF Analysis

A lumbar puncture to evaluate leptomeningeal involvement with lymphoma should be recommended in patients with:
Samples should be sent for cell count, protein and 5-10 cm³ should be sent for cytologic examination.

**Gallium Scan**

A total body gallium scan should be performed in all patients being treated with curative intent, particularly those who would be considered for salvage therapy and stem cell transplantation if not in complete remission after initial therapy.

**PET Scan**

Positron emission tomography (PET) imaging with 2-fluoro-2-deoxy-D-glucose (FDG) is a new imaging modality that shows promise in the management of lymphoma. While early studies suggest that staging with PET compares favourably with conventional staging with CT and gallium scans [3], PET appears to play a greater role in assessment of incomplete responses to therapy than in initial staging.

**HIV Serology**

B-cell lymphoma is the most common malignancy associated with HIV infection. As HIV lymphoma is treated differently and risk factor assessment is imperfect in identifying HIV positive patients, most patients with DLBCL should undergo HIV serology testing at diagnosis. If serology testing is not planned, patients should be asked in detail regarding risk factors, including blood transfusion, intravenous drug use and sexual contact with persons who may have been at risk for HIV, and testing should be performed in patients with risk factors.

**Cardiac Assessment**

A cardiac assessment should be performed in all patients potentially eligible for anthracycline-based chemotherapy (such as CHOP-R). MUGA scan or 2D-echocardiogram should be performed in all patients with a history of:

- Age > 60
- Hypertension
- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular disease
- Angina
- Cardiac arrhythmia
- Myocardial infarction

Anthracyclines should be **used with caution** in patients with an EF < 45%, recent MI (< 3 months) or severe arrhythmia.

**Staging & Prognosis**

Patients with DLBCL should be staged according to both the Ann Arbor and IPI staging systems [4]. The Ann Arbor staging system continues to be in use in DLBCL. This system provides limited prognostic information, but is of use in determining therapeutic management. All patients should have an Ann Arbor stage assigned.
Stage Definition

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region or a single extranodal site.</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph nodes on the same side of the diaphragm or localized involvement of an extra lymphatic organ or site and one or more lymph nodes on the same side of the diaphragm.</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm that may also be accompanied by involvement of the spleen or by localized involvement of an extra lymphatic organ or site or both.</td>
</tr>
<tr>
<td>IV</td>
<td>Diffused or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.</td>
</tr>
</tbody>
</table>

The absence or presence of fever > 38.5 °C, drenching night sweats, and/or unexplained weight loss of 10 percent or more body weight in the six months preceding admission are to be denoted in all cases by the suffix A or B respectively.

The International Prognostic Factor Index

The International Prognostic Factor Index (IPI) provides more precise and reproducible prognostic information than the Ann Arbor stage, but does not distinguish patients eligible for combined modality therapy for localized disease [5]. The IPI stage is dependent on five prognostic factors: Age, Ann Arbor stage, Performance status, LDH and number of extranodal sites.

Outcome According to Risk Group Defined by the International Index and the Age-Adjusted International Index

<table>
<thead>
<tr>
<th>Risk Group</th>
<th># of Risk Factors</th>
<th>Distribution of patients (%)</th>
<th>CR Rate (%)</th>
<th>2-yr Rate</th>
<th>5-yr Rate</th>
<th>2-yr Rate</th>
<th>5-yr Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Index, all patients (n = 2031)*</td>
<td>Low (L)</td>
<td>0, 1</td>
<td>35</td>
<td>87</td>
<td>79</td>
<td>70</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>Low-intermediate (LI)</td>
<td>2</td>
<td>27</td>
<td>67</td>
<td>66</td>
<td>50</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>High-intermediate (HI)</td>
<td>3</td>
<td>22</td>
<td>55</td>
<td>59</td>
<td>49</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>High (H)</td>
<td>4, 5</td>
<td>16</td>
<td>44</td>
<td>58</td>
<td>40</td>
<td>34</td>
</tr>
</tbody>
</table>

| Age-adjusted Index, patients ≤ 60 (n = 1274)* | Low (L) | 0 | 22 | 92 | 88 | 86 | 90 | 83 |
| | Low-intermediate (LI) | 1 | 32 | 78 | 74 | 66 | 79 | 69 |
| | High-intermediate (HI) | 2 | 32 | 57 | 62 | 53 | 59 | 46 |
| | High (H) | 3 | 14 | 36 | 61 | 58 | 37 | 32 |

| Age-adjusted Index, patients > 60 (n = 761)* | Low (L) | 0 | 18 | 91 | 75 | 46 | 80 | 56 |
| | Low-intermediate (LI) | 1 | 31 | 71 | 64 | 45 | 68 | 44 |
| | High-intermediate (HI) | 2 | 35 | 56 | 60 | 41 | 48 | 37 |
| | High (H) | 3 | 16 | 36 | 47 | 37 | 31 | 21 |

*The total of patients includes the 1385 in the training sample and the 646 in the validation sample.
†The total of the patients in the two analysis with the age-adjusted index includes four more patients than the total in the analysis with the international index because all the data necessary for these four patients to be included in the age-adjusted analysis (which evaluated fewer variables) were available.

Clinical Characteristics of Patients ≤ and > 60 Years of Age

<table>
<thead>
<tr>
<th></th>
<th>≤ 60 yrs (%)</th>
<th>&gt; 60 yrs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced stage (III/IV)</td>
<td>64</td>
<td>68</td>
</tr>
<tr>
<td>Elevated serum LDH</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>Non-ambulatory performance status (2-4)</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>&gt; 1 Extraneodal disease site</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

The IPI has been evaluated in patients receiving R-CHOP and remains predictive of survival in such patients [6]. In a retrospective review of 365 patients from the British Columbia Cancer Agency, a revised R-IPI that divided patients into 3 groups (very good risk-0 RF; good risk 1-2 RF; and poor risk 3-5 RF) was reported to be more discriminatory than the conventional IPI. This awaits prospective validation from other groups and our Centre will continue to use the conventional IPI groupings. The reported survival from this study is:

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>No. of IPI Factors</th>
<th>% Patients</th>
<th>4-year PFS %</th>
<th>4-year OS%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard IPI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0, 1</td>
<td>28</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>Low-intermediate</td>
<td>2</td>
<td>27</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>High-intermediate</td>
<td>3</td>
<td>21</td>
<td>57</td>
<td>49</td>
</tr>
<tr>
<td>High</td>
<td>4, 5</td>
<td>24</td>
<td>51</td>
<td>59</td>
</tr>
<tr>
<td><strong>Revised IPI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>0</td>
<td>10</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Good</td>
<td>1, 2</td>
<td>45</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>Poor</td>
<td>3, 4, 5</td>
<td>45</td>
<td>53</td>
<td>55</td>
</tr>
</tbody>
</table>

Other Prognostic Factors

A variety of other factors have been demonstrated to predict outcome of patients with DLBCL. Gene expression profiling by cDNA microarray is an exciting technique with the potential to improve our understanding of the pathogenesis of lymphoma. A germinal center B-cell like expression profile has been found to predict for improved outcome and provides prognostic value independent of the IPI [7]. This technique is complex and resource intensive and is not in routine clinical use. Other favourable prognostic factors include germinal center phenotype by immunohistochemistry (defined by expression of bcl-6 and CD10) [8]. Expression of bcl-2 [8, 9], on the other hand predicts poor outcome. These factors are not routinely used in clinical practice and should not be used to make treatment decisions in individual patients.

Management of Localized Disease

The management of patients with limited stage DLBCL remains controversial. In fact, the terms “limited stage” or “localized” are used variably. It is clear that patients with stage I or II disease do better than those with stage III or IV disease [10], however, patients with limited stage disease are not a homogeneous group [11], and those with stage II or bulky disease (mass > 10 cm or 1/3 of maximal trans-thoracic diameter) are generally recognised to have worse outcomes than those without these characteristics [12]. In particular, patients with bulky stage II disease have been reported to have an outcome comparable to those with advanced stage disease [12].

Patients with stage II disease do worse than those with stage I and the modified IPI can predict outcome in this group of patients (considering stage II to be a risk factor). In one study, 5-year overall survivals range from 94% for those with 0 IPI risk factors to only 50% for those with 3 factors [11]. Patients with bulky stage II disease have been reported to have an outcome comparable to those with advanced stage disease [12].
Patterns of practice in managing patients with limited stage disease differ between Europe and North America. In Europe, the practice of treating patients in a manner similar to advanced stage disease (omitting radiotherapy) is common, based principally on two trials by the GELA suggesting that the addition of radiotherapy did not improve outcome [13, 14]. In North America, practice is driven by two cooperative group studies. The first was a RCT from the SWOG group comparing 3 cycles of CHOP plus involved field radiotherapy to 8 cycles of CHOP [10, 11]. This trial initially demonstrated that combined modality therapy was associated with superior survival. However, with longer follow-up, the failure-free and overall survival advantage associated with combined modality therapy (CMT) has not been sustained. In particular, late relapses and lymphoma deaths after 5 years were more common in those treated with abbreviated CMT, suggestive that a minimum dose of anthracycline-based chemotherapy may be necessary for prolonged remission in most patients.

An analysis of a modified IPI (considering stage II as an adverse factor) in the SWOG study has identified a group with a favourable prognosis for whom three cycles of chemotherapy and radiation may be adequate. Those with no stage-modified IPI risk factors had a 5-year overall survival of 94% with CMT, while those with at least one risk factor (age > 60, LDH elevated, performance status > 2, or stage II disease) had a 5-year overall survival was only 70% [11, 15, 16].

The Relationship Between Clinical Stage, Risk Factors and Outcome for Patients with Limited Disease [17]

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Stage-Modified IPI Risk Factors*</th>
<th>Treatment</th>
<th>5-Year Median Survival</th>
<th>Limited Stage</th>
<th>Proposed Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I, IE</td>
<td>0</td>
<td>CHOP(3) + RT</td>
<td>&gt; 90%</td>
<td>Yes</td>
<td>Very limited</td>
</tr>
<tr>
<td>I, IE, IIE (no bulky II)</td>
<td>≥ 1</td>
<td>CHOP(3) + RT</td>
<td>70%</td>
<td>Yes</td>
<td>Limited</td>
</tr>
<tr>
<td>Bulky II, Bulky IIE</td>
<td>Any</td>
<td>CHOP(8)</td>
<td>50%</td>
<td>No</td>
<td>Advanced</td>
</tr>
</tbody>
</table>

Abbreviations: IPI, International Prognostic Index; CHOP(3) + RT, cyclophosphamide, doxorubicin, vincristine, prednisone, plus radiotherapy; CHOP(8), CHOP given in eight cycles.

*Stage-modified International Prognostic Index (IPI) adverse risk factors include: any stage II disease, age > 60 years, serum lactase dehydrogenase above normal limits, and performance status 0-1.

In an RCT from the ECOG, all individuals with limited stage disease received 8 cycles of CHOP followed by a randomisation in complete responders to radiation vs. observation. The addition of radiation was associated with an improvement in disease-free survival, but not overall survival in this population [18].

While little direct evidence exists confirming the benefit of rituximab in this patient population, the Cancer Care Ontario Hematology DSG has recommended that rituximab be given with CHOP (CHOP-R), largely on the strength of the MINT trial [19] which included a significant number of patients with limited stage disease and the BCCA experience [6, 20].

Patients with localized DLBCL felt to be poor candidates for anthracycline-based chemotherapy may be treated with radiation alone with reasonable probability of long-term survival. Outcomes with this approach have been best for patients with stage IA disease and tumour bulk of ≤ 2.5 cm [21]. Such patients should receive **3000 cGy in 15 fractions** to the volume of presumed microscopic disease and a boost of **600 cGY in 3 fractions** to the involved volume.

Recommendations

- Most patients with stage I-IIA DLBCL should receive combined modality therapy

- Such patients should be seen in consultation by a radiation oncologist early in order to plan radiotherapy soon after completion of chemotherapy

- **Favourable risk (0-1 IPI risk factors) non-bulky disease:** Three cycles of CHOP-rituximab (Appendix B) should be administered at 3 weekly intervals. Response will be assessed by CT scan and gallium scan 2 weeks after the third cycle. Patients in CR/CRU after chemotherapy will receive **3000 cGy in 15 fractions**. Patients who have had a reduction in tumour mass > 50% (PR) and have a residual
abnormality < 5 cm will receive involved field RT to sites of pre-chemotherapy disease to **3000 cGy in 15 fractions** with a boost of **600 cGy in 3 fractions** to post-chemotherapy residual disease. Patients who have not achieved at least a PR or who have residual bulk ≥ 5 cm will receive 3 further CHOP-R and will be re-staged after 6 cycles with a plan to proceed to radiation with doses described above.

- **Patients with ≥ 2 IPI risk factors and/or bulk disease:** Should receive 6 cycles of CHOP-R rather than 3, followed by IF-RT as above.
- In situations in which involved field radiation is felt to be associated with excess toxicity, 6 cycles of CHOP-R rather than a combined modality approach should be offered.
- Patients felt to be at high-risk from anthracycline-based chemotherapy should receive local irradiation alone.

### Extranodal Disease

Approximately one third of DLBCL arises from extranodal tissue [22]. This can occur in any tissue and there are numerous small reports suggesting particular biology or clinical behavior for lymphomas arising from specific organ systems. Increasingly, larger single or multi-center series are shedding greater light on disease biology. A recently published single center series which reports the clinicopathological features of 382 patients with DLBCL according to primary site and provides insight into some of these differences [22]. The International Extranodal Lymphoma Study Group (IELSG) is a unique cooperative group dedicated to increasing understanding of these entities. Their publications on lymphomas of the brain, intravascular lymphoma, gastric and non-gastric MALT among others can be downloaded from [www.ielsg.org](http://www.ielsg.org). We will briefly highlight certain sites that require special considerations:

1. **Bone**
   - Patients with lymphoma arising from bone are reported to have a favorable prognosis [23]. Patients may present with single (monostotic) or multiple lesions. Surgery should be limited to biopsy only. Five-year survivals of 85-90% have been reported with the most favorable results reported for patients under age 40 and those who received combined modality therapy. Patients should receive 3-6 cycles of CHOP-R followed by radiation. Radiation should be administered to sites of disease defined by pre-chemotherapy MRI. A dose of **3600 cGy in 18 fractions** should be administered to sites of pre-chemotherapy disease with a boost to **800 cGy in 4 fractions** to post-chemotherapy residual.

   **Breast**
   - Primary breast lymphoma is rare, accounting for < 1% of lymphomas [24]. Some reports have suggested a tendency for recurrences in the breast and central nervous system. However, the evidence that patients with DLBCL presenting in the breast have outcomes different from other sites is weak and does not support treating patients with primary breast lymphoma differently from patients with other extranodal sites [22, 25-27]. The International Extranodal Lymphoma Study Group has completed a study of patients with primary diffuse large B-cell lymphoma of the breast that is expected to be published shortly ([www.ielsg.org/publicfr.html](http://www.ielsg.org/publicfr.html)). Patients with breast lymphoma should receive 3 cycles of CHOP-R followed by involved field radiation. Radiation should be administered to sites of pre-chemotherapy disease to a dose of **3000 cGy in 15 fractions**. The target volume will include the entire breast in patients with CS IE disease and the breast and regional nodes in those presenting with CS IIE disease.

2. **CNS – see policy for primary CNS Lymphoma**

3. **Gastric**
   - Gastric lymphoma may arise as a de novo extranodal diffuse large cell lymphoma or as a large cell transformation from a low grade gastric MALT. Without pathologic documentation, these may be indistinguishable. Gastric lymphoma is typically diagnosed by endoscopic biopsy. Gastric resection is not recommended unless mandated by refractory bleeding or obstruction as studies suggest inferior outcome for patients treated with surgical resection [28, 29]. Patients with gastric lymphoma should receive 3 cycles of CHOP-R followed by involved field radiation. Six cycles of CHOP-R may be considered for patients with initial bulk or incomplete response. Radiation should be delivered to sites of pre-chemotherapy disease to a dose of **3000 cGy in 15 fractions**. The target volume should include the
entire stomach in patients with CS IE disease, and the stomach and regional nodes in those presenting with CS IIE disease. Patients deemed unfit for chemotherapy may be treated with conformal radiotherapy to the stomach and regional nodes to a dose of **36 – 40 Gy in 18 – 20 fractions** depending on bulk.

4. **Small Bowel**
Surgical resection is typically undertaken as patients generally present with acute abdominal complications such as bleeding or obstruction. Patients will typically be treated with 6 cycles of CHOP-R.

5. **Testis**
Patients with testicular lymphoma appear to have a poor prognosis compared to most other extranodal presentations [30]. Even in patients with favourable risk IPI, outcome appears worse than for comparable patients with nodal lymphomas [30]. There is a tendency for relapse in the contra-lateral testis, other extranodal sites, and in the central nervous system. CNS relapses are more typically in the parenchymal brain as opposed to leptomeningeal in distribution.

Patients with testicular lymphoma should undergo orchietomy. CT scan of the brain and lumbar puncture should be performed in all patients [30]. Patients should be treated with 6 cycles of CHOP-R followed by radiation to the scrotum to a dose of **3000 cGy in 15 fractions**. CNS prophylaxis in the form of 2 cycles of high-dose methotrexate given after the second and third cycle of CHOP should be offered to patients under age 70 with good performance status and normal renal function. In patients over the age of 70 and those with poor performance status or renal dysfunction, the risks of high-dose methotrexate generally outweigh the benefits, and no prophylaxis will routinely be recommended.

6. **Thyroid**
The outcome of patients with thyroid lymphoma is reported to be inferior to other extranodal sites, principally due to higher mortality unrelated to disease [21]. Data presented in abstract form from the IELSG suggest superior outcome for patients undergoing surgical resection followed by chemotherapy +/- radiation. We recommend that patients be considered for surgical resection followed by 3 cycles of CHOP-R and consolidation radiation to a dose of **3000 cGy in 15 fractions**.

7. **Waldeyer’s Ring**
Lymphomas arising from Waldeyer’s ring are not technically extranodal [22]. These are reported to have a favorable prognosis with a tendency to present with localized favorable risk disease. Patients should be treated with 3 cycles of CHOP-R followed by radiation utilizing parotid-sparing IMRT to a dose of **3000 cGy in 15 fractions**.

---

**Management of Advanced Stage Disease**

CHOP is as effective as any other studied regimen and is associated with less toxicity than most second or third generation regimens [31]. The addition of rituximab to chemotherapy is the subject of CCO practice guideline 6-8 (see CCO-PEBC EBS 6-8 at [www.cancercare.on.ca](http://www.cancercare.on.ca)). Five randomized trials report improved event-free survival with the addition of Rituximab to CHOP or CHOP-like chemotherapy [19, 32-35]. Only one trial conducted in patients with HIV lymphoma did not demonstrate improved outcome [36]. The addition of rituximab to CHOP or CHOP-like chemotherapy is associated with an 11%-13% increase in 2-year survival, with the effect observed in all risk groups.

Patients with advanced stage de novo or transformed DLBCL who are candidates for aggressive therapy with curative intent should be treated with CHOP-rituximab. Patients will be scheduled to receive six cycles at 3-week intervals (Appendix B). Response will be assessed clinically at each cycle and by CT scan after the 3rd – 4th cycle. Patients progressing on therapy or who fail to achieve a 50% reduction in disease bulk after the 3rd – 4th cycle of chemotherapy will be considered refractory to therapy and should be considered for salvage therapy (see Management of Relapsed Disease, page 9) [37]. At the completion of the 6th cycle of treatment patients will be completely re-staged including bone marrow and/or lumbar puncture if initially positive. The practice of giving two additional cycles of CHOP-R to patients with a suboptimal response to 6 cycles of therapy is of questionable benefit and will not routinely be done. For such patient confirmation of response by biopsy or PET scanning is preferable.
High-Risk Patients

Results of initial therapy in patients with high-risk disease according to the IPI are sub-optimal. Four-year survival of only 59% is reported for such patients with CHOP-R [6]. These patients are ideal candidates for new experimental therapy, such as transplantation and biologic therapy. At present, however, such patients should be treated with CHOP-R in the absence of clinical trials. Patients not felt to be candidates for curative treatment should be treated conservatively including radiation or palliative chemotherapy as appropriate.

Dose Modification of CHOP-R

The intent is to deliver full dose chemotherapy for all patients; however, dose modification may be needed for selected patients. Doses will not be modified for advanced age alone. Patients with hematologic impairment due to marrow involvement with lymphoma should also receive full dose therapy, potentially with growth factor support (see Growth Factor Support below). Patients with cytopenias due to other reasons should be treated with caution. Patients with hepatic dysfunction may require modification of Adriamycin and vincristine doses. Those with bilirubin levels of > 50 should not receive either agent, while those with bilirubin levels of 20-50 should have 50% dose reduction. Patients with significant peripheral neuropathy, and those at risk due to diabetes, alcoholism, or other factors should receive vincristine with caution, but will not routinely be dose-reduced.

Growth Factor Support

The DSG believes that dose intensity is important in patients receiving CHOP-R with curative intent [38]. Patients who develop febrile neutropenia with any cycle of treatment, as well as those who have a neutrophil count below 1.1 prior to cycle 2-6 of treatment should be started on G-CSF for all remaining cycles. Dose delays and reductions should be kept to a minimum. Patients with a high IPI (3+ risk factors) have an increased risk of febrile neutropenia and should be considered for primary prophylaxis with G-CSF (see Febrile Neutropenia Policy and CCO-PEBC EBS 12-2 & 6-9 at www.cancercare.on.ca).

Antibiotic Prophylaxis

Antibiotic prophylaxis is not routinely indicated for patients undergoing CHOP-R. It can be considered for selected patients, but must be weighed against the potential development of antibiotic resistance, as well as increased difficulty using outpatient therapy for febrile neutropenia.

Assessment of Response

Responses are classified according to the Cheson criteria (Appendix C). These criteria are currently in evolution, with new PET-based criteria being proposed [39]. For the time being, we will continue to use the 1999 criteria. A complete response (CR) requires complete disappearance of detectable clinical and radiologic evidence of disease and disappearance of all disease-related symptoms and normalization of biochemical abnormalities. A CRU involves ≥ 75% reduction in lymph node masses with a normal or indeterminate bone marrow. CR and CRU are both considered to be complete responses.

Responses will be felt to be incomplete if the above criteria are not met. Wherever possible, a biopsy should be performed to confirm incomplete response. Alternatively, PET scanning should be considered where biopsy cannot be easily done and demonstration of residual disease would alter management (CCO-PEBC EBS 6-20 at www.cancercare.on.ca). Patients with PET positive disease following chemotherapy do poorly and should be considered for high-dose therapy and autologous stem cell transplantation.

Radiotherapy (CR or Good PR)

Involved field radiation (3000 cGy/15 for CR, 3600 cGy/18 for PR) should be considered upon completion of chemotherapy for patients with bulky disease at presentation (> 10 cm) or if local relapse would compromise organ function (such as spinal cord, cauda equina, biliary tree or ureter).
Management of Incomplete Responders

Patients who progress while on therapy or who fail to achieve a complete response do poorly [37]. Where possible, incomplete response should be confirmed by biopsy or PET scan. Outcome for such patients with conventional chemotherapy is very poor. Outcome with high-dose therapy and stem cell transplantation is poorer than for patients with chemotherapy sensitive relapsed disease, largely due to difficulty responding to pre-transplant salvage chemotherapy. Patients who are potentially eligible for intensive therapy and stem cell transplantation should begin salvage chemotherapy (see Management of Relapsed Disease) (Appendix B) [40]. Patients who are not transplant candidates should be managed palliatively. Involved field radiation should be considered in such patients with persistent disease that can readily be encompassed in a radiation field. Aggressive salvage chemotherapy alone is not considered curative in this setting, and as such the palliative benefit of such treatment must be weighed against the heavy toxicity of such regimens. Substantial palliative benefit can often be obtained with less toxicity with less aggressive palliative regimens (such as oral VP-16 + prednisone [Appendix B]).

Follow-Up

10–50% of patients with DLBCL who enter remission will relapse, usually within the first 12–18 months. Patients who achieve a CR should be followed every 4 months for the first 2 years and every 6-12 months thereafter. Assessment should consist of:

- History & Physical
- CBC & differential
- Serum LDH, creatinine

Patients in PR may need more frequent follow-up.

Imaging

Routine surveillance imaging is an inefficient means of identifying relapse. Imaging should be performed in patients with symptoms suggestive of relapse or in selected patients felt to be at particularly high risk of recurrence.

Management of Relapsed Disease

Despite improvements in upfront therapy, recurrent lymphoma remains an important problem. In patients with evidence of recurrent disease, histologic confirmation is strongly recommended given the potential to recur with indolent histology disease. This should be considered particularly in patients with minimally symptomatic recurrence and those who recur late (> 2 yrs) after initial treatment. Recurrences with indolent histology should be managed as indolent lymphomas.

Patients with DLBCL who relapse with aggressive histology after anthracycline-based chemotherapy have a short survival [41]. The main prognostic factors are duration of first complete response and IPI at relapse. There is evidence that high-dose therapy and autologous stem cell transplantation (ASCT) improves survival in patients with chemosensitive relapse [41]. For this reason, ASCT should be recommended to patients of younger age (< 65) with good performance status and no limiting co-morbid medical problems. Patients should be referred to a transplant centre early for assessment.

Many salvage chemotherapy combinations have been developed to get patients to transplant in this disease (DHAP, ESHAP, MINIBEAM and MIME) [42]. These regimens share many features such as the absence of anthracycline and the use of agents such as VP-16, cis-platinum and cytosine arabinoside. These regimens are associated with response rates of 25–40% and there is no compelling evidence that one is superior to any other. The addition of rituximab to such salvage regimens has not been demonstrated to improve overall response rates and is not funded through the Ontario New Drug Funding Program. The GDP regimen is currently being tested against DHAP in a large international randomized trial (NCIC-CTG LY.12). Patients eligible, should be offered enrolment on this important study. For patients not enrolled in clinical trials GDP...
will be recommended as first-line salvage for most patients. DHAP is an alternative regimen, but requires hospital admission (Appendix B). Two cycles of either regimen will be given at 3-4 week intervals as hematologic recovery allows. Patients must have a response to chemotherapy in order to proceed to transplant. If no response is seen to first-line salvage, palliative regimens such as VP-16 and prednisone should be offered. The response rate to second-line salvage regimens is low (< 20%) with few patients achieving sustained remissions post-transplant. For this reason, these regimens should not routinely be offered in such cases.

In addition, radiation may be offered in selected patients undergoing high-dose therapy to treat areas of initial bulk or residual disease. Such treatment should be discussed with the transplant team and may take place before or after high-dose therapy.

Patients not eligible for high-dose therapy should be managed palliatively with involved field radiation in cases of localized relapse and palliative systemic therapy with transfusion, steroids and/or palliative chemotherapy such as VP-16 and prednisone to control symptoms. There is no role for intensive platinum-based regimens in such cases.

Special Considerations

Elderly Patients

Elderly patients with DLBCL do substantially worse than younger patients. The lower response rate to therapy appears to relate to both a more aggressive behaviour, as well as increased difficulty delivering treatment.

Two approaches have been used to improve outcome in older patients. One strategy has been to aggressively maintain or increase dose intensity using growth factor support if necessary, while a second approach has been to attenuate doses of therapy to limit toxicity [43]. The strategy of dose reduction has been associated with less toxicity, but also shorter survival [44] (See CCO-PEBC EBS 6-7 at www.cancercare.on.ca). Older patients with good performance status and minimal co-morbidities should be offered full-dose curative treatment.

Prophylaxis and Treatment of Leptomeningeal Lymphoma

CNS relapse is relatively common in DLBCL and is uniformly associated with short survival [45]. Factors that predict a higher likelihood of CNS relapse are extranodal involvement (especially blood, bone marrow, testicular, sinus orbits), high LDH, stage IV disease, epidural lymphoma. All patients with such risk factors should have CSF sampled by LP with 10 cm³ sent for cytology. Prophylaxis with intrathecal methotrexate is of questionable utility. Patients felt to be at high-risk of isolated CNS recurrence should be offered two cycles of high-dose methotrexate chemotherapy given after the second and third cycle of CHOP-R.

Patients with known leptomeningeal disease should undergo brain and spinal MRI to identify focal deposits, which can be treated with radiation. Patients with known CNS involvement (leptomeningeal or intraparenchymal) should receive CHOMP with IV Rituximab (Appendix B) and intensive intrathecal chemotherapy. Patients with evidence of gross disease on MRI scan or CT scan of the neural axis should be treated with involved field radiotherapy.

References

3. Maillard, I., et al, Comparison of conventional staging studies and FDG-PET imaging in Hodgkin's


