

## CHAPTER 13 AGGRESSIVE LYMPHOMA

### 13.1 Introduction

This diverse group of lymphomas has in common an aggressive clinical behaviour. These lymphomas are very sensitive to chemotherapeutic agents, rendering them curable in a significant proportion of patients.

The pathological entities in this group of diseases are included in the mature B-cell and mature T-cell neoplasms in the WHO classification.<sup>1</sup>

They are:

- B-cell:
  - 1 Diffuse large B-cell lymphoma (DLBCL)
  - 2 Mantle cell lymphoma
  - 3 Mediastinal (thymic) large B-cell lymphoma
  - 4 Intravascular large B-cell lymphoma
  - 5 Primary effusion lymphoma
- T-cell:
  - 6 Angioimmunoblastic T-cell lymphoma
  - 7 Peripheral T-cell lymphoma, unspecified (PTCL)
  - 8 Extranodal NK/T-cell lymphoma, nasal type
  - 9 Hepatosplenic T-cell lymphoma
  - 10 Anaplastic large-cell lymphoma (ALCL)

### 13.2 Epidemiology

The aggressive lymphomas comprise about 50% of all lymphomas. The most common subtype is DLBCL, which constitutes 30–40% of all adult lymphomas.<sup>2</sup> The median age of patients is in the 60s, but the range is broad and the incidence increases with age.

The proportion of the specific subtypes according to the WHO classification is as follows:

DLBCL	30.6%
Mantle cell lymphoma	6.0%
Mediastinal LBCL	2.4%
PTCL	7.6%
ALCL	2.4%

### 13.3 Clinical presentation

Patients typically present with a rapidly enlarging mass at a nodal or extranodal site. Up to 40% of cases present with extranodal disease. The most common extranodal site is the gastrointestinal tract

(stomach or ileocaecal region). Virtually any extranodal site may be a primary location, including skin, bone, central nervous system, testis, and breast.

In general, DLBCL arises *de novo*, but in some cases, DLBCL arises as a result of transformation from an indolent lymphoma, for example, follicular lymphoma, CLL/SLL, marginal zone B-cell lymphoma, or nodular lymphocyte predominant Hodgkin lymphoma. Patients who are immunodeficient have an increased risk of developing DLBCL. In these cases the tumours are frequently positive for the Epstein-Barr virus (EBV).

### 13.4 Staging

The staging process is similar to that recommended for Hodgkin lymphoma (see Chapter 11):

- 1 History and Physical Examination
- 2 Radiology: chest x-ray, CT scan of chest, abdomen and pelvis
- 3 Pathology: full blood count, routine biochemistry including LDH and uric acid
- 4 Bone marrow biopsy
- 5 Diagnostic lumbar puncture in certain circumstances (paranasal sinus presentation, testicular lymphoma, involvement of bone marrow, more than two adverse parameters according to IPI)
- 6 Functional imaging — gallium and/or PET scanning. Evolving data suggest that PET scanning may be more sensitive than gallium scanning for the staging of patients with lymphoma<sup>3</sup>
- 7 MUGA scan or echocardiogram where appropriate
- 8 Stage according to Ann Arbor system (see Table 11.1)

#### 13.4.1 International prognostic index

Pretreatment prognostic factors are critical in determining treatment and predicting outcome. The International Prognostic Index (IPI) was developed from a study of 2031 patients with aggressive lymphoma treated with a doxorubicin-based chemotherapy regimen. Five pre-treatment characteristics were found to be independent predictors. These are: age ( $\leq 60$  versus  $>60$ ), stage I or II versus stage III or IV, number of extranodal sites involved ( $\leq 1$  versus  $>1$ ), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus  $\geq 2$ ), serum LDH (normal versus greater than normal).<sup>4</sup>

Table 13.1 demonstrates the value of the index, which should be determined for each patient prior to treatment.

**Table 13.1 International Prognostic Index**

Risk group	Number of risk factors	% of patients	CR rate (%)	5-year survival (%)
Low	0–1	35	87	73
Low–intermediate	2	27	66	51
High–intermediate	3	22	54	43
High	4–5	16	34	26

Recently, cDNA microarray profiling has been shown to predict treatment outcome through the identification of specific patterns of gene expression.<sup>5</sup> DLBCL can be divided into prognostically significant subgroups with germinal centre B-cell-like (GCB), activated B-cell-like (ABC), and type 3 gene expression profiles.<sup>6,7</sup>

The GCB group has significantly better survival than the ABC group. The type 3 is heterogeneous, but has a poor outcome similar to the ABC group. Recently, immunostains have been used to determine the GCB and non-GCB subtypes of DLBCL and predict survival similar to the cDNA microarrays.<sup>8</sup>

## 13.5 Treatment of aggressive lymphoma

### 13.5.1 General principles

Where feasible, patients should have their treatment planned in a multidisciplinary process. This should comprise, at a minimum, haematologist/medical oncologist and radiation oncologist.

The treatment plan should reflect histological subtype, stage, IPI, age, co-morbidities and performance status.

The treatment strategy in patients with aggressive lymphoma, where feasible, is to cure the patient with initial therapy. The main treatment modality is combination chemotherapy, while in some patients the addition of radiation therapy provides additional benefit. Surgery has little role in this disease.

Relapse or failure to achieve complete response to therapy is associated with a poor outlook.

## 13.6 Diffuse large B-cell lymphoma (DLBCL)

### Summary of clinicopathological findings

Clinical	Nodal or extranodal (any site). Rapidly expanding mass at any site. Often disseminated.
Morphology	Diffuse or partial, may be interfollicular or sinusoidal. <i>Variants:</i> centroblastic (inc. multilobated form), immunoblastic, T-cell/histiocyte-rich, anaplastic.
Immunophenotype	Mostly SIg+(M>G>A), cytoIg+ in plasmacytic/immunoblastic types. CD19+, CD20+, CD22+, CD79a+. CD30+ in most anaplastic cases and some non-anaplastic cases. Occasionally CD5 or CD10+ve. <i>Bcl-2</i> +ve in minority of cases. <i>Bcl-6</i> +ve. Proliferation index (Ki-67) is high, >90% in rare cases. <i>Variants:</i> (a) Plasmablastic EBER+, CD20-, CD45-, CD138+. (b) DLCL with expression of full length IgA+, SIg+, ALK-, CD30-, CD45+/-, EMA+, CD4+, CD57+.
Genetics	Mostly post germinal centre t(14;18) in 20–30% bcl-6 gene involved in 30% These have prognostic significance.

The management of DLBCL has provided a model for curative cancer therapy integrating chemotherapy and radiotherapy. The following principles of management may also be applied to the other aggressive lymphoma entities.

### 13.6.1 First-line treatment of patients with DLBCL

#### *Early-stage disease*

About 15–20% of patients with DLBCL present with localised disease defined as stage I or II. Before 1980, radiation therapy alone was used as the primary treatment for patients with localised DLBCL. Approximately 50% of patients with stage I and 20% of patients with stage II disease were alive without recurrence at five years.<sup>9</sup> In a retrospective study from Stanford University, local control rates of 70–80% were achieved at doses ranging from 20 Gy to 50 Gy.<sup>10</sup> In patients with limited disease and normal LDH, local radiotherapy alone is reported to produce 70–80% five-year freedom from progression, and can be considered in patients unsuitable for chemotherapy. Most relapses occur outside the radiation field.<sup>11</sup>

Several large phase II trials have shown that combined-modality therapy using chemotherapy in addition to involved-field radiotherapy produced high, long-term, disease-free survival rates. In most of these studies, the radiation fields were reduced and the doses of radiation were also lower than when radiation is used as the sole treatment modality. The largest series, using a combination of doxorubicin-based chemotherapy regimens and involved-field radiation, produced complete remission rates of close to 100%, and five-year survival rates of over 80%.<sup>12,13</sup>

Several prospective randomised trials have been performed by cooperative groups addressing the role of radiation therapy in localised DLBCL. The Southwest Oncology Group (SWOG) randomised 401 patients with stage I and non-bulky stage II aggressive lymphomas (75% DLBCL) to three cycles of CHOP followed by involved-field radiation therapy to a dose of 40–55 Gray or to eight cycles of CHOP alone.<sup>14</sup> Both the PFS and OS at five years were superior in the combined modality arm (PFS 77% versus 64%,  $P=0.03$ ; OS 82% versus 72%,  $P=0.02$ ). Severe toxicity and cardiac toxicity were higher in the patients receiving CHOP alone. In an update of this study, with a median follow up of eight years, the authors reported a higher relapse rate and lymphoma-related deaths occurring between five and ten years for the combined modality arm, such that the curves overlap at seven years for PFS, and at nine years for OS.

The Eastern Cooperative Oncology Group (ECOG) treated 352 patients with stage I (bulky >10 cm mass or extranodal) or stage II disease with eight cycles of CHOP. The 215 patients achieving a CR were randomised to no further treatment or involved-field radiotherapy to a dose of 30 Gy for patients in CR or 40 Gy for those in PR. The disease-free survival and overall survival at five years were superior for the combined chemoradiotherapy arm (73% versus 58%,  $P=0.03$  and 84% versus 70%,  $P=0.06$ ) respectively. At ten years, the DFS was in favour of the combined therapy arm ( $P=0.05$ ), but there was no difference in OS,  $P=0.24$ .<sup>15,16</sup>

The Groupe d'Etudes des Lymphomes des l'Adultes (GELA) reported a study in patients >60 years with stage I and II aggressive lymphoma and an age-adjusted IPI of zero. Patients were randomised between four cycles of CHOP versus four cycles of CHOP plus involved-field radiation therapy to 40 Gy. There were no differences in CR rates, five-year EFS or OS. However, for patients older than 70 years, the overall survival was better in the group receiving CHOP alone.<sup>17</sup>

Another study from GELA compared three cycles of CHOP followed by 30–40 Gy involved-field radiotherapy with the chemotherapy regimen ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone), followed by consolidation chemotherapy with methotrexate, ifosfamide, etoposide and cytarabine. In 631 patients with low-risk, localised aggressive lymphoma EFS and OS were 74% and 80% for CHOP plus radiation versus 83% and 89% for the complex sequential chemotherapy regimen ( $P=0.004$  and  $P=0.02$  respectively).<sup>18</sup>

Guideline — Recommended treatment for localised aggressive lymphoma	Level of evidence	Refs
Patients with non-bulky stage I, with normal LDH and ECOG PS $\leq$ 1, should be treated with three cycles of CHOP and involved-field radiation therapy to a dose of 30–40 Gy.	II-III	9–14
Patients with bulky stage I, stage II, high LDH, ECOG $\geq$ 2 and/or three or more disease sites should be treated with 6–8 cycles of CHOP followed by involved-field radiation to 30–40 Gy.	II	15, 16
Radiotherapy may be unnecessary in elderly patients with localised aggressive lymphoma.	II	17
Patients with low-risk localised aggressive lymphoma may be treated with more intensive sequential chemotherapy, omitting radiation therapy.	II	18

### ***Initial treatment of advanced-stage DLBCL***

For patients with advanced-stage disease (stages III and IV), combination chemotherapy with curative intent is the most effective treatment. Prior to the development of multi-agent chemotherapy, the median survival of patients with DLBCL was less than one year.

Combination chemotherapy has been shown to have high efficacy in aggressive lymphoma. The CHOP regimen was first described in 1975. It has been studied extensively in single arm and randomised clinical trials. The standard CHOP regimen consists of cyclophosphamide 750 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, vincristine 1.4 mg/m<sup>2</sup> (capped at 2.0 mg), and prednisone (or prednisolone) 100 mg/day for five days (no standard dose, some trials use 40 mg/m<sup>2</sup>). Treatments are given every 21 days.<sup>19</sup>

Attempts were made to increase the CR rate and decrease the relapse rate by developing second and third generation regimens based on the concept of dose intensity. They were designed to deliver the greatest number of active drugs (generally six to eight) at the highest possible drug dose per unit time. These regimens included m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone), ProMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide, etoposide, followed by cytarabine, bleomycin, vincristine and methotrexate), and MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin). However, randomised trials comparing CHOP to second and third generation regimens failed to show any benefit of the newer regimens. The landmark intergroup SWOG/ECOG phase III trial comparing the above four regimens showed no difference in CR, progression-free (estimated five year of 33–38%) or overall survival (estimated five year of 45–46%).<sup>20</sup> A meta-analysis of these trials confirmed the equivalence of CHOP to other regimens.<sup>21</sup>

There are no randomised trials comparing the efficacy and toxicity of six versus eight cycles of CHOP. A common practice is to give two further cycles of CHOP after documentation of CR, with a minimum of six cycles, as most patients achieve CR after four.

### ***Modified CHOP regimens***

Modified CHOP regimens (CHOP-like) have generally attempted to reproduce or improve on the efficacy of CHOP with a reduction in toxicity. In these regimens, doxorubicin in CHOP was substituted by either another anthracycline or the anthracenedione mitoxantrone. A number of randomised phase III trials comparing these regimens to CHOP have shown equivalent efficacy and toxicity.<sup>22–24</sup>

Guideline — Recommended treatment for advanced-stage DLBCL	Level of evidence	Refs
CHOP chemotherapy is equivalent in outcome to other chemotherapy regimens with decreased toxicity.	II	19–24

### ***Rituximab with standard CHOP***

Rituximab is a chimeric human/murine IgG1 monoclonal antibody that binds specifically to the B-cell surface antigen CD-20. It acts by inducing both complement-mediated and antibody-dependent cytotoxicity. It also induces apoptosis and sensitised chemoresistant human lymphoma cell lines to cytotoxic chemotherapy.<sup>25</sup>

Rituximab alone at a dose of 375 mg/m<sup>2</sup> per week has a response rate of 31% in relapsed DLBCL.<sup>26</sup>

The addition of rituximab to CHOP has been widely explored in clinical trials. High response rates have been reported in phase II studies. In a phase II trial of 33 patients treated with R-CHOP for six cycles, the CR rate was 76%, with 88% progression-free at a median follow up of 31 months.<sup>27</sup>

The GELA group performed a randomised phase III trial in 399 elderly (age range 60–80 years), previously untreated patients with advanced-stage DLBCL of standard-dose CHOP given every 21 days, versus the same regimen plus rituximab (375 mg/m<sup>2</sup>) on day one of each of eight cycles of treatment (R-CHOP). Patients were stratified by age-adjusted IPI scores (0–1 versus 2–3). The CR/CRu rate increased from 63% to 76% (p=0.005). The EFS was significantly longer in the R-CHOP arm as a result of lower rates of relapse and progression (P<0.001). The two-year OS was 57% in the CHOP arm and 70% in the R-CHOP arm (P=0.007). No increase in toxicity was noted and the addition of rituximab did not compromise the dose-intensity of CHOP. The benefit of R-CHOP was consistent across all subgroups of patients tested, including both low-risk (IPI 0–1) and high-risk (IPI 2–3) patients, but was greatest in patients with low-risk disease. An update of this trial presented at the ASH meeting in December 2003 showed that the results hold up with longer follow up. Whether these results can be extrapolated to young patients with advanced-stage disease, or to patients with early-stage disease, will require further clinical trials.<sup>28,29</sup>

The addition of rituximab to chemotherapy appears to have the greatest impact in DCBCL that over-expresses *bcl-2*. Several studies have implicated *bcl-2* over-expression as a poor prognostic factor in DLBCL. In the GELA study, two-year EFS and OS rates improved from 32% to 58% and from 48% to 67% respectively in the R-CHOP arm. There was no difference in EFS or OS rates between CHOP and R-CHOP in *bcl-2* negative patients.<sup>30</sup>

A second large randomised study was presented by Haberman et al. at the ASH meeting in December 2003.<sup>31</sup>

This was a North American intergroup study in 632 patients older than 60 years who were randomised to either R-CHOP or CHOP, followed by a second randomisation in patients achieving CR or PR to observation or maintenance rituximab. The overall response rates (ORR) were 77% with R-CHOP and 76% with CHOP (P=0.76). With a median follow up of 2.7 years, the TTF favoured R-CHOP (P=0.025), but there was no difference in OS (P=0.25). TTF also favoured maintenance rituximab (P=0.01), but there was no difference in OS (P=0.67). The schedule of rituximab used in this study differed from those in the GELA study. Patients received fewer courses of rituximab during induction CHOP. These factors may account for the differences in results between this study and the GELA study.

Guideline — Recommended treatment for advanced-stage DLBCL	Level of evidence	Refs
The addition of rituximab to CHOP is superior to CHOP in patients older than 60 years.	II	25–31

### *Dose intensified CHOP-like regimens*

#### *High-dose CHOP or CHOP-like regimens*

Few studies have looked at increasing doses of the drugs in the CHOP regimen. The Australasian Leukaemia and Lymphoma Group (ALLG) performed a randomised trial in patients with aggressive lymphoma, stage I bulky, II–IV, comparing CEOP (cyclophosphamide 750 mg/m<sup>2</sup> epirubicin 75 mg/m<sup>2</sup>), to high-dose CEOP (cyclophosphamide 1500 mg/m<sup>2</sup> epirubicin 150 mg/m<sup>2</sup>) with G-CSF. In a study of 250 patients, there was no difference in CR rate, failure-free or overall survival, despite a mean 78% increase in dose intensity of the two drugs, cyclophosphamide and epirubicin.<sup>32</sup>

Guideline — Chop chemotherapy	Level of evidence	Refs
Dose escalation of CHOP or CHOP-like regimens does not improve overall survival.	II	32

#### *Dose-dense regimens (including CHOP-14 and R-CHOP-14)*

Gisselbrecht and colleagues treated 162 poor-prognosis patients with the LNH-84 induction regimen (cyclophosphamide, vindesine, bleomycin, prednisone, and methotrexate) and either doxorubicin or mitoxantrone. By using higher doses of cyclophosphamide and doxorubicin, and reducing the interval between cycles to two weeks, this regimen represents a two-fold increase in relative dose intensity over CHOP. Patients randomised to receive adjunctive G-CSF (5 µg/kg/day) were less likely to experience neutropenia or documented infections, and received significantly greater dose intensity, compared with patients not treated with G-CSF (93% versus 80%; p=0.0001). However, the CR rate and three-year survival were similar between the two groups. Adjunctive use of G-CSF facilitates the use of dose-intensified chemotherapy regimens.<sup>33</sup>

The results from two (NHL-B1 and NHL-B2) German High Grade Non-Hodgkin's Lymphoma Group studies have recently been published. Dose intensification was achieved by reducing the interval (dose-dense) between doses or by adding an extra drug to a combination regimen.

The data from NHL-B2 study suggest that reducing the interval between doses yields improved survival in elderly patients (61–75 years) with aggressive lymphoma. Final results were reported on 689 eligible patients of all IPI risk groups, who were randomised to the standard three-weekly CHOP regimen (CHOP-21), CHOP plus etoposide (CHOEP-21), or either regimen administered every two weeks (CHOP-14 or CHOEP-14) in all arms for six cycles. Shortening the treatment interval to two weeks was facilitated by the use of adjunctive G-CSF. Six hundred and eighty nine (689) patients were available for analysis. CR rates favoured CHOP-14. Five-year EFS and OS were 32.5% and 40.6%, respectively for CHOP-21, and 43.8% and 53.3% respectively for CHOP-14. In a multivariate analysis, the relative risk reduction was 0.66 (p=0.003) for EFS and 0.58 (p<0.001) for OS.<sup>34</sup>

The results of the NHL-B1 are also available. This study looked at patients between 18 and 60 years with good prognosis lymphoma (normal LDH) and randomised them equally to CHOP-21, CHOEP-21, CHOP-14, CHOEP-14, for six cycles, as per NHL-B2. Shortening of the treatment interval to two weeks was facilitated by the use of adjunctive G-CSF. Seven hundred and ten (710) patients were available for analysis. CHOEP achieved better CR rates (87.6% versus 79.4%: p=0.003) and five-year

EFS (69.2% versus CHOP 57.6%;  $p=0.004$ ), while interval reduction (i.e. 14-day regimens) improved OS ( $p=0.05$ ;  $p=0.044$ ) in the multivariate analysis.<sup>35</sup>

Guideline — CHOP Chemotherapy and Etoposide	Level of evidence	Refs
Etoposide added to CHOP therapy in low-risk patients younger than 60 years is superior in time to treatment failure than CHOP.	II	35

Gregory et al. in 2002 demonstrated in 120 patients (18–84 years) that CHOP-14 could be administered every fourteen days with prophylactic G-CSF support. Eight five per cent of the planned cycles were given on time at full dose. Haematologic toxicity was significant, but the tolerable with no treatment-related deaths and responses rates were comparable to CHOP-21.<sup>36</sup>

Wolf and Bentley<sup>37</sup>, in Australia, have also demonstrated that pegfilgrastim can be used safely and efficaciously to support CHOP-14.

At the 2003 meeting of ASCO, the Senior Adult Care Task Force of the National Comprehensive Cancer Network (NCCN) advisory panels, Hotta et al. presented the Japan Clinical Oncology Group phase III study, JCOG9809, in which patients with advanced aggressive lymphoma were randomised between standard CHOP (S-CHOP) and CHOP given every two weeks (Bi-CHOP). Both arms received eight cycles of chemotherapy. There was no improvement in two-year progression-free survival or overall survival. The trial was terminated early after the first 286 patients were enrolled. It is not clear why this trial should have shown conflicting results to the German trial, as the full study has not been published. Patients' ages ranged from 17 to 69 years (median 57), and both normal and high LDH were included. The actual delivered dose intensity in the Bi-CHOP arm is uncertain.<sup>38</sup>

The GELA group has recently reported a study comparing eight cycles of CHOP to ACVBP (doxorubicin 75 mg/m<sup>2</sup> day one, cyclophosphamide 1200 mg/m<sup>2</sup> day one, vindesine 2 mg/m<sup>2</sup> days one and five, bleomycin 10 mg days one and five, every two weeks for four cycles, followed by sequential consolidation therapy (methotrexate with leucovorin, ifosfamide, etoposide and ara-C). There were 635 eligible patients aged 60–69 years, with at least one adverse prognostic factor by age-adjusted IPI. Despite higher toxicity, the ACVBP regimen was superior to standard CHOP in both event-free and overall survival. The CR rate was similar (56 versus 58%), but the EFS and OS at five years were better in the ACVBP arm (39 versus 29% and 46 versus 38% respectively).<sup>39</sup>

These studies of increased dose density represent methods in which dose-intensity chemotherapy can be delivered by decreasing the interval between cycles. The administration of dose-dense chemotherapy requires haematopoietic growth factor support from the first cycle of chemotherapy and every subsequent cycle.

### Key point

It is difficult to offer a definitive guideline given the rapidly emerging new information about the adoption of dose-dense CHOP-like regimens with haemopoietic growth factor support. Participation is recommended in clinical trials where possible, or development of treatment policies in specialised units as new information becomes available.

### Role of consolidative radiotherapy

Several retrospective studies have examined the impact of involved-field radiotherapy in patients with advanced-stage aggressive lymphoma who responded to CHOP or CHOP-like chemotherapy. These studies suggest that radiotherapy improved local control and freedom from progression in patients with tumour size of larger than 4–6 cm. One prospective, randomised trial in patients with stage IV

diffuse large-cell lymphoma and tumour masses >10 cm showed an improvement in disease-free (five-year rates 72% versus 35%,  $P<0.01$ ) and overall survival (five-year rates 81% versus 55%,  $P<0.01$ ).<sup>40,41</sup>

### *Use of haemopoietic growth factors*

A 2004 report from the Cochrane Database entitled 'Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma' reviews 12 randomised studies with 1823 patients. This review concludes that when G-CSF given prophylactically does not affect tumour response, time to treatment failure or overall survival, there is a statistically significant reduction in the risk of neutropenia, febrile neutropenia and infection rates, leading to a potential positive impact for patients.<sup>42</sup>

However, as new information emerges from the dose-dense studies described above, recommendations for the use of G-CSF in these circumstances will need to be revised. This issue is discussed further in the next section.

### *Special populations — the aged*

Balducci and Repetto report in 2004 that the benefits of prophylactic use of G-CSF in managing neutropenia in elderly patients with lymphoma have been shown in four studies. In these studies, a total of 656 patients receiving CHOP or CHOP-like therapy were randomised to G-CSF or placebo. The primary endpoints of these studies were grade 3/4 neutropenia and incidence of infection. The results in all four studies showed statistically significant reduction in grade 3/4 neutropenia and infection rates in the G-CSF treated groups.<sup>43</sup>

In a trial performed by the Dutch haemato-oncology association (HOVON) group in patients aged 65–90 years with stage II–IV aggressive lymphoma, patients were randomised between standard CHOP every 21 days and CHOP plus G-CSF on days 2–11 of each cycle. In 389 eligible patients, the relative dose intensities (RDIs) of cyclophosphamide and doxorubicin were significantly higher in the G-CSF arm (96% versus 94% and 95% versus 93% respectively). However, there was no significant difference in CR rate (55 versus 52%) or OS at five years (22 versus 24%). There was also no difference in the incidence of infections or duration of hospitalisation. Thus, based on this study, the prophylactic use of G-CSF with standard CHOP is not justified.<sup>44</sup>

Published practice guidelines recognise the elderly as a population at increased risk for chemotherapy-induced neutropenia. ASCO and the European Organisation for Research and Treatment of Cancer (EORTC) recommend the use of prophylactic colony-stimulating factor (CSF) in elderly cancer patients receiving myelosuppressive chemotherapy.

In a published letter to the *Journal of Clinical Oncology*, Balducci and Lyman identified elderly ( $\geq 70$  years) patients as a special population at risk for chemotherapy-induced neutropenia.<sup>45</sup>

The ASCO 2000 guidelines for the use of CSFs recommend that prophylactic CSFs be considered in certain circumstances in patients who are at higher risk for chemotherapy-induced neutropenia infectious complications. In addition to older age, risk factors include pre-existing neutropenia due to disease, extensive previous chemotherapy, or previous irradiation to the pelvis or other areas containing large amounts of bone marrow; history of recurrent febrile neutropenia while receiving chemotherapy of similar or lower dose intensity; or potentially enhancing the risk of serious infection (e.g. poor performance status and more advanced cancer, decreased immune function, open wounds, or active tissue infections).<sup>46</sup>

The EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer conclude:

...the Working Party recommends the use of prophylactic G-CSF to support the administration of planned doses of chemotherapy on schedule and reduce the incidence of chemotherapy-induced neutropenia, febrile neutropenia and infections in elderly patients receiving myelotoxic chemotherapy.<sup>47</sup>

## Key points

### Special populations — the aged

Prophylactic G-CSF should be considered in elderly patients and also in patients thought to be at high-risk, which is defined as:

- pre-existing neutropenia due to disease
- extensive previous chemotherapy or significant previous radiation therapy
- history of recurrent febrile neutropenia while receiving chemotherapy of similar or lower-dose intensity
- at risk for serious infection (e.g. poor performance status, decreased immune function, open wounds, or active tissue infection)

Careful consideration should be given in the use of anthracyclines in this group of patients with potential cardiac dysfunction.

### *Front-line high-dose therapy with stem cell support*

Early attempts at utilising high-dose chemotherapy (HDCT) and autologous stem cell transplantation derived from observations from the PARMA study in which patients with relapsed aggressive lymphoma salvaged with HDCT and ASCT demonstrated improved survival rates compared to those who had received conventional salvage chemotherapy.<sup>48</sup> This study defined high-dose therapy as the treatment of choice for patients with relapsed aggressive lymphoma sensitive to salvage chemotherapy.

A number of studies have examined the role of high-dose therapy to consolidate an initial response to chemotherapy. These studies have been characterised by significant variability with respect to the timing of the HDCT, the amount of induction therapy administered (i.e. abbreviated or full-course induction), and in their recruitment of different IPI risk cohorts. Accordingly, the studies have yielded conflicting results.

The LNH87-2 trial of the GELA group randomised 1043 patients less than 55 years of age to one of AVVB or NCVB followed by four additional cycles of cyclophosphamide, vindesine, bleomycin, prednisone and intrathecal methotrexate. Patients achieving a CR were then randomised to either HDCT and SCT or additional cycles of sequential chemotherapy. In the initial analysis there were no differences in the three-year OS or DFS.<sup>49</sup> However, a subsequent retrospective analysis of 236 patients who were IPI high-intermediate or high-risk showed a superior eight-year DFS (55% versus 39%,  $P=0.02$ ) and OS (64% versus 49%,  $P=0.04$ ) for the high-dose therapy arm.<sup>50</sup>

In another GELA study reported by Gisselbrecht et al., 397 patients under 60 years of age with poor prognosis aggressive lymphoma and two to three risk factors were randomised to a five-drug chemotherapy regimen or a shortened treatment program with three cycles of escalated doses of cyclophosphamide, epirubicin, vindesine, bleomycin and prednisone followed by high-dose chemotherapy and autologous stem cell transplantation. The five-year DFS and OS was inferior for the group receiving transplantation.<sup>51</sup>

A recent meta-analysis of eleven randomised studies of autologous stem cell transplantation, suggested a benefit in terms of improved overall survival for HDCT/ASCT over and above

conventional therapy only among those patients with high or high–intermediate IPI, and who had received prior full-course (versus abbreviated) induction therapy.<sup>52</sup>

At present, up-front, high-dose therapy with autologous stem cell transplantation cannot be recommended, even for poor-risk patients, outside of a clinical trial.<sup>53</sup>

Guideline — Front-line high-dose therapy with stem cell support	Level of evidence	Refs
Up-front high-dose therapy with autologous stem cell transplantation cannot be recommended outside of a clinical trial.	II	48–53

### ***Central nervous system prophylaxis***

Central nervous system (CNS) relapse of lymphoma is usually fatal despite therapy, and effective prophylaxis is desirable. It occurs in between 5% and 30% of patients with aggressive lymphoma. The incidence is insufficient to justify universal CNS prophylaxis. Many attempts have been made to identify factors associated with a high rate of CNS relapse. There is general agreement that patients with testicular and paranasal sinuses involvement should receive prophylaxis. For other groups, there are two large retrospective studies for guidance. Involvement of more than one extranodal site and a raised LDH was the only independent predictor of CNS recurrence.<sup>54</sup> Patients with both risk factors had a 17.4% incidence of CNS recurrence at one year compared to a 2.8% incidence if one or neither of these factors was present. A study by the HOVON group reported the risk of CNS recurrence to be related to the IPI score. Low-risk patients had a 0% incidence; high-risk had a 27% risk of CNS recurrence.

The optimal prophylactic therapy is unclear. In most cases, intrathecal chemotherapy with methotrexate or cytarabine is used. However, a 26% rate of CNS relapse in high-risk patients given prophylactic treatment with intrathecal chemotherapy has been reported.<sup>55</sup>

### ***Response assessment***

- 1 Physical examination and appropriate radiological tests should be performed after 2–4 cycles of CHOP and 3–4 weeks after the last cycle to assess response.
- 2 If a bone marrow biopsy is initially abnormal it should be repeated at the end of treatment.
- 3 Standard response criteria should be used to assess response categories.
- 4 The use of functional imaging (gallium-59, or FDG-PET) is often of value in assessing response, particularly in the evaluation of a residual mass after chemotherapy.
- 5 Many residual abnormal masses on CT scan do not contain any viable tumour tissue. If clinically indicated, biopsy of a residual mass should be considered. A percutaneous fine-needle aspirate or core biopsy under radiological guidance is often of value in this situation. It is possible that PET scanning may avoid this issue.
- 6 Patients who have not achieved a complete response (CR) should be evaluated for early salvage treatment regimens. Evolving opinions suggest that PET scanning, even after as few as one to two cycles, may predict likelihood of CR. This is an area for continuing study.

### ***Follow up***

There are few studies examining the value of follow-up strategies on the early detection and treatment of recurrence of lymphoma. The European Society of Medical Oncology recommends the following follow-up schedule.<sup>56</sup>

- 1 History and physical examination every three months for two years, every six months for three more years, and then annually. High-risk patients may require more frequent assessments.
- 2 Blood count and LDH at three, six, twelve and twenty-four months, the subsequently only if there is clinical suspicion of relapse.
- 3 Evaluation of thyroid function (TSH) in patients receiving neck irradiation at one, two and five years.
- 4 Screening for breast cancer in women who received chest irradiation at a premenopausal age, starting at 40–50 years.
- 5 Adequate radiological examinations at six, twelve and twenty-four months, by CT scan when indicated by site of disease.

There is little evidence to support these recommendations for follow-up procedures. In the retrospective studies that have been reported in the literature, only a minority of recurrences were detected by routine laboratory or radiologic studies.

### **13.6.2 Treatment of patients with relapsed aggressive lymphoma**

More than 50% of patients with aggressive lymphoma are either primary refractory or, more often, relapse after a complete response to their initial treatment. For these patients, high-dose therapy with stem cell transplantation has been demonstrated to have the greatest potential for cure.<sup>48</sup> However, this treatment approach is generally restricted to patients who are sensitive (achieve a CR or PR) to second-line or salvage chemotherapy. In general, patients who are refractory to second-line chemotherapy should not be offered stem cell transplantation except in the context of a clinical trial. These patients have a very poor prognosis.

Where relapse occurs late (more than twelve months after initial treatment) patients should, wherever possible, have a repeat biopsy to exclude the possibility of a follicular lymphoma. Early relapse does not generally require a rebiopsy.

Staging procedures should follow the guidelines for newly diagnosed disease. The IPI should be calculated, as this has prognostic value. The cumulative dose of anthracyclines used during first-line therapy should be calculated. If further anthracyclines are to be used, an echocardiogram or MUGA scan for the quantification of the left ventricular ejection fraction should be done.

There are no randomised trials comparing salvage regimens. Commonly used regimens studied in phase II trials are dexamethasone, high dose cytarabine and cisplatin (DHAP or DHAC), etoposide, cisplatin, high dose cytarabine and methylprednisolone (ESHAP), ifosfamide, carboplatin and etoposide (ICE), and etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin (EPOCH). Response rates to salvage chemotherapy generally range between 45% and 70%, with CR rates of 25–40%. In the absence of a clinical trial, the choice of salvage regime is up to the individual physician. Some regimens, for example, ICE, also enable the collection of adequate numbers of peripheral blood stem cells.

Recently, many salvage regimens have incorporated the anti-CD20 monoclonal antibody rituximab. In one study, the CR rate in patients treated with R-ICE was significantly higher than with historical controls treated with ICE.<sup>57</sup>

There is no current established role for allogeneic stem cell transplantation in relapsed or refractory aggressive lymphoma. This procedure could be considered in individual patients with relapsed disease, who are young and have a histocompatible donor.

## 13.7 Mantle cell lymphoma

### Summary of clinicopathological findings

Clinical	Older patients, male predominance, stage III or IV. Hepatosplenomegaly, lymphadenopathy and marrow involvement. GI involvement common.
Morphology	Mantle zone, nodular or diffuse patterns. No proliferation centres. Monomorphous small to medium-sized cells with irregular nuclear contours. Absence of large follicle centre cells, prolymphocytes, immunoblasts or para-immunoblasts. Scattered epithelioid histiocytes. Variants: blastoid; (classic, lymphoblastoid and pleomorphic)
Immunophenotype	SIgM and IgD+. CD5+ in most cases, CyclinD1+, CD43+, FMC7+, <i>bcl-2</i> +. CD23-, CD10-, <i>bcl-6</i> -, CD21, CD23OR CD35 dispersed FDC meshworks reflecting architectural pattern.
Genetic	Pre-germinal centre cell. <i>t</i> (11:14)(q13;q32) in most cases ( <i>PRAD1</i> , <i>bcl-1</i> ). Other cytogenetic changes often associated with blastic variants.

#### 13.7.1 Prognosis

Mantle cell lymphoma (MCL) was recognised as a distinct clinicopathological entity in 1991.<sup>58</sup> It is now accepted that this form of lymphoma has among the poorest long-term outcome of all B-cell lymphomas. However, a small proportion of patients with MCL may have an indolent course, and not initially require therapy. Attempts at prediction of outcome are under investigation with the use of new prognostic markers.<sup>59–63</sup>

#### Key point

Identification of indolent subgroups of mantle cell lymphoma using appropriate indices and markers is emerging as an important issue.

#### 13.7.2 Non-intensive therapy

The BNLI report of 65 cases of MCL treated with non-intensive therapy (radiotherapy, COP, or chlorambucil) showed that such approaches were associated with median progression-free (PF) and overall survival (OS) times of 2 and 4.75 years respectively. Forty of these patients received second-line therapy, with a median overall survival of 25 months. None were alive at ten years.<sup>64</sup>

The rare patient with localised disease may, however, be cured by involved-field radiotherapy alone.<sup>64</sup>

These poor results have led to the investigation of novel treatment strategies in MCL.

The addition of anthracyclines appears to add little, with CR rates of 20–30% and similar over-all outcomes reported in a number of phase II studies.<sup>65–67</sup>

#### 13.7.3 Role of rituximab

The addition of rituximab to CHOP and the fludarabine, cyclophosphamide and mitoxantrone (FCM) regimen have been reported to improve responses in recently reported randomised studies.

The German Low Grade Lymphoma Study Group (GLSG) performed a prospective randomised trial of CHOP versus CHOP plus rituximab (CHOP-R) in 122 patients with newly diagnosed stage III or IV MCL. CHOP-R was superior to CHOP in terms of overall response rate (94% versus 75%), CR rate (34% versus 7%), and time to treatment failure (median 21 months versus 14 months), but not

progression-free or overall survival.<sup>68</sup> The authors suggest that CHOP-R may serve as a new baseline for advanced-stage MCL. They acknowledge, however, that post-induction therapy needs to be further improved given the lack of impact on overall survival.

A second prospective randomised study of the GLSG compared FCM with rituximab FCM in patients with relapsed or refractory MCL and follicular lymphoma. Only 48 patients with MCL could be evaluated. This study showed the FCM plus rituximab regimen was superior in terms of overall response (58% versus 46%), CR (29% versus 0%), progression-free survival and strikingly, overall survival.<sup>69</sup>

Both studies suffer from their small size and the low CR rates in the standard arms. Their findings need to be confirmed.

Phase II studies of novel agents such as thalidomide and the proteasome inhibitor bortezomib have suggested significant activity in MCL.<sup>70–72</sup>

Intensification of chemotherapeutic regimens has been investigated using a variety of approaches. Such strategies have limited applicability, given the age of patients with MCL—the median is 60–65 years.<sup>64</sup>

### 13.7.4 Intensive and high-dose chemotherapy

The hyper-CVAD regimen produced a 68% CR rate in a small single institution study of newly diagnosed patients over the age of 65 years.<sup>73</sup>

A number of phase II studies utilising autologous transplantation have been reported.<sup>74–84</sup>

Three recently published studies are described below:

- A French multicentre study enrolled 28 patients with newly diagnosed MCL into a program of sequential CHOP, DHAP and then TBI-cytarabine-melphalan-conditioned peripheral blood stem cell autologous transplant (auto-PBSCT). A high CR rate (84%) and long PFS (75% at a median follow up of four years) were reported.<sup>74</sup>
- An Italian multicentre study enrolled 28 newly diagnosed patients to receive an intensive regimen following standard induction. The R-HDS regimen included cyclic high-dose cyclophosphamide (7 gm/m<sup>2</sup>), high-dose cytarabine (24 gm/m<sup>2</sup>) and two cycles of high-dose melphalan (180 mg/m<sup>2</sup>). The program was supported by auto-PBSCT and six doses of rituximab were administered. Once again, a high CR rate (100%) and high OS and EFS at 54 months of 89% and 79% were seen.<sup>75</sup>
- A small study utilising I-131-labeled anti-CD20 antibody followed by high-dose cyclophosphamide and etoposide supported with the infusion of autologous PBSC reported similar response and survival rates.<sup>76</sup>

These studies suggest that the use of HDT with auto-PBSCT may prolong survival in MCL. A similar conclusion was drawn from a registry-based analysis of 195 patients with MCL transplanted and reported to the European Group for Blood and Marrow Transplantation and the International Bone Marrow Transplant Registry. Best outcomes were seen with patients transplanted in first CR or those with responsive disease.<sup>85</sup>

A single phase III study addressing the role of autologous transplantation has been reported. This study, performed by the European MCL network, randomised newly diagnosed responsive patients to receive either two cycles of Dexamethasone-BEAM followed by a Cy/TBI-conditioned auto-PBSCT, or a total of eight cycles of CHOP followed by interferon maintenance. One hundred and twenty two (122) patients were randomised. While response rates were higher and PFS was longer in patients randomised to the HDT arm, OS at three years was not prolonged.<sup>86</sup>

Taken together, these data suggest that selected patients may benefit from autologous transplantation but this strategy cannot be recommended as part of standard therapy at this time. Data confirming that increased response rates translate to prolongation in survival are awaited.

The role of allogeneic transplantation remains uncertain.

The experience with myeloablative allo-HSCT is limited to case reports or small series. Long-term survival has been reported.<sup>87</sup>

The data concerning non-myeloablative allografts allow the conclusion that there seems to be a graft versus MCL effect. The durability of responses is unclear, as is the optimal transplant protocol.<sup>87</sup>

### Key point

The optimal therapy of patients with mantle cell lymphoma is unclear at present. Given the poor outcomes with conventional therapy, novel approaches should be considered and implemented preferably in the context of clinical trials. Such patients should optimally be managed in specialised centres.

## 13.8 Mediastinal (thymic) large B-cell lymphoma

### Summary of clinicopathological findings

Clinical	Female predominance, third to fifth decades. Localised anterior mediastinal mass. Dissemination is extranodal: kidney, adrenal, liver skin and brain.
Morphology	Diffuse, sclerotic and compartmentalised like carcinoma. Large cells with clear cytoplasm.
Immunophenotype	CD19+, CD20+, CD45+. Ig and HLA-DR may be -ve. CD5-, CD10-. Often CD30 weakly +ve.
Genetics	Hyperdiploid, gains in 9p and <i>REL</i> amplification. Over-expression of <i>MAL</i> gene.

Primary mediastinal B-cell lymphoma (PMBCL) with sclerosis is a distinctive subtype of non-Hodgkin's lymphoma. It has unique clinicopathologic aspects and aggressive behaviour. This is a subtype of DLBCL arising in the mediastinum of putative thymic B-cell origin. It typically arises in relatively young patients (20–50 years), with a female preponderance. Patients present with localised disease and clinical features related to a large anterior mediastinal mass, sometimes with superior vena caval syndrome. The cells express B-cell markers such as CD19 and CD20. CD10 and CD5 are usually negative.

In a large retrospective review by the International Extranodal Lymphoma Study Group of 426 patients from 20 institutions with PMLCL, the authors found that MACOP-B appeared superior to other chemotherapy programs, including CHOP.<sup>88</sup> This retrospective study strongly suggests that MACOP-B (or similar third-generation chemotherapy regimens such as VACOP-B) plus radiation therapy represents the best therapeutic option for most of these patients. The long-term overall survival is as high as 70–75%. On the other hand, patients with predictive factors of poor outcome are likely candidates for high-dose sequential chemotherapy plus autologous stem cell transplantation.

## 13.9 Treatment of aggressive T-cell lymphoma

T-cell lymphomas are uncommon in Western countries, and constitute about 15–20% of the aggressive lymphomas. They are more common in Asia. Most patients present with nodal

involvement, but any site can be affected. Patients often have generalised disease with infiltrates in the bone marrow, liver, spleen and extranodal tissues.

There are no standard treatment protocols for aggressive T-cell lymphomas. In general, treatment approaches similar to those used for aggressive B-cell lymphomas have been used. Several studies have reported inferior outcome for patients with aggressive T-cell lymphomas when compared to B-cell lymphomas when stratified for IPI. However, other studies have found that, stage for stage, the outcome of T-cell and B-cell diffuse large-cell lymphomas was similar.<sup>89-92</sup>

More intensive therapies are under investigation.

### Summary of clinicopathological findings: peripheral T-cell NOS

Peripheral T-cell lymphomas that are not otherwise specified (peripheral T-cell NOS) are the most common form of T-NHL (~50%) in Western countries.

Clinical	Adults > children. Often disseminated nodal disease +/- extranodal, including skin, marrow. Aggressive, <30% five-year survival.
Morphology	Medium to large cells, some with clear cytoplasm; prominent venules; admixed inflammatory cells. Some have mainly atypical small cells. Variants: Lennert's lymphoma (epithelioid histiocyte-rich) and T-zone lymphoma with preserved follicles.
Immunophenotype	CD3+, variable pan-T loss, most CD4+, CD30+/- mainly in large-cell type; CD56+ and cytotoxic phenotype rare. EBV+/- in bystander cells or large B cells.
Genetics	Clonal rearrangements of TCR genes. No consistent cytogenetic abnormalities; complex karyotypes.

### 13.10 Anaplastic large-cell lymphoma

There are clinico-epidemiological differences between ALK protein positive (ALK+) or negative (ALK-) cases. This category specifically describes cases of T-cell or null cell anaplastic large-cell lymphoma (ALCL).

Clinical	Bimodal age distribution. ALK+ cases first three decades of life, M>F; ALK- cases in later life. Most have B symptoms but low IPI scores, stage III or IV disease involving nodes and extranodal sites (chiefly skin, bone, soft tissue, lung, liver, gut; marrow involvement subtle — up to 30% if immunostains used). Excellent prognosis — 75% overall survival and 56% failure free survival for all ALCL-T/null cases in the Lymphoma Classification Project, the best overall survival and failure-free survival of any large-cell lymphoma. ALK+ ALCL has better survival than ALK- ALCL. <sup>93</sup>
Morphology	Cohesive growth of cells, diffuse and sinusoidal distribution. 'Hallmark cell' present in all morphological variants — large cell, eccentric reniform or horseshoe-shaped nucleus, prominent but not 'inclusion-like' nucleoli, paranuclear eosinophilic region. Common (70%), lymphohistiocytic (10%) and small cell (5–10%) variants recognised, among other less common forms.
Immunophenotype	T-cell or null-cell phenotype and CD30+ are definitional. ALK protein+ (60–85%) in nuclear and cytoplasmic, cytoplasmic only, or membrane-restricted pattern. Extensive pan-T antigen loss; CD3e+/-; CD2+/-, CD4+/-; usually EMA+, CD45+, CD45RO+ and CD43+; Cytotoxic protein+ in >50%; clusterin+.
Genetics	Up to 90% have clonally rearranged TCR genes. EBER negative. Several cytogenetic abnormalities involving the ALK gene (2p23) described. t(2;5)(p23;q35) most common involving nucleophosmin gene. Other partner genes may be TPM3 (1q25), TFG (3q21), ATIC (2q35), CLTCL (17q11-ter), MSN (Xq11-12).

### 13.11 Other variants of aggressive T-cell lymphomas

Rare entities include angioimmunoblastic T-cell lymphoma, hepatosplenic gamma/delta T-cell lymphoma and enteropathy-type (intestinal) T-cell lymphoma. At present, there are no data to support an approach different from that recommended for B-cell lymphomas. If possible, these patients should be entered into clinical trials.

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