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POSITION PAPER

Diffuse large B-cell lymphoma: a consensus practice statement from the Australasian Lymphoma Alliance

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype, accounting for 30–40% of lymphoma diagnoses. Although aggressive, cure is achievable in approximately 60% of cases with primary chemoimmunotherapy, and in a further substantial minority by salvage therapy and autologous stem cell transplantation. Despite promising activity in early phase clinical trials, no intensified or novel treatment regimen has improved outcomes over R-CHOP21 in randomised studies. However, there remain several areas of controversy including the most appropriate prognostic markers, central nervous system prophylaxis and the optimal treatment for patients with high-risk disease. This position statement presents an evidence-based synthesis of the literature for application in Australasian practice.

Introduction

Current controversies in diffuse large B-cell lymphoma (DLBCL) include identification of biomarkers for prognostication and treatment selection and management of specific risk groups such as limited stage disease, high-risk disease and those at risk of central nervous system (CNS) dissemination. This practice statement provides healthcare professionals with an evidence-based approach to the investigation and management of DLBCL in the Australasian setting. Specific subtypes of extranodal disease are outside the scope of this statement.

Methodology

This Consensus Practice Statement was undertaken by a panel of lymphoma experts with particular interest in DLBCL under the auspices of the Australasian Lymphoma Alliance (ALA) in accordance with the ALA Consensus Practice Statement development policy (Supporting Information Tables S1,S2).

Incidence and aetiology

The incidence of non-Hodgkin lymphoma in Australia is approximately 20 cases per 100 000 person-years and is increasing, with DLBCL accounting for 30–40%.[1] Most

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patients are aged >50 years at diagnosis, with a slight male predominance. The aetiology is largely unclear, although immunosuppression and Epstein–Barr virus play a role in certain cases.[2]

Diagnosis

Definitive diagnosis of DLBCL relies on biopsy. Excisional node biopsy is preferred, although core biopsy may be adequate in many cases.[3] Histologically, normal lymph node architecture is usually completely or partially effaced by a diffuse proliferation of large atypical lymphoid cells, which morphologically may be classified as centroblastic, immunoblastic or anaplastic.[4] Immunohistochemistry (IHC) and flow cytometry confirm the lineage of the neoplastic lymphoid cells. The neoplastic B cells are positive for B-cell markers, including CD20, which has therapeutic implications.[4] Other important IHC markers are shown in Table 1. The definitive final pathological classification of DLBCL, not otherwise specified relies on the exclusion of high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBL-DH or HGBL-TH) by performing fluorescence *in situ* hybridisation (FISH). Approximately 8% of cases resembling DLBCL morphologically are HGBL-DH when investigated for the presence of these gene rearrangements and the preferred approach is to test all cases.[5,6] If limited resources preclude routine FISH studies, testing only CD10 positive cases that concurrently express MYC and BCL2/BCL6 protein by IHC will capture most HGBL-DH while reducing the number of DLBCL proceeding to FISH.[6,7] Cases undergoing FISH may also utilise a stepwise approach by first testing *MYC* and, if present, subsequently testing for *BCL2* and *BCL6*. It is worth noting that FISH does not capture all cases with a HGBL-DH gene signature, which is prognostically relevant, although gene expression profiling (GEP) is not routinely available.[8]

Table 1 Recommended immunohistochemical work-up of diffuse large B-cell lymphoma (DLBCL)

Marker	% Positive	Utility
CD20	>95%	Confirm B-cell lineage, predicts sensitivity to rituximab
PAX5	>95%	Confirm B-cell lineage
CD10	30–50%	Suggests germinal centre subtype
MUM1	35–65%	Suggests post-germinal centre subtype (in absence of CD10)
BCL6	60–90%	Suggests germinal centre subtype (in absence of MUM1)
C-MYC	~30–40%	Confers inferior prognosis when expressed with BCL2
BCL2	~50–60%	Confers inferior prognosis when expressed with C-MYC
EBER-ISH	~5% in Western population	
CD5	5–10%	Defines CD5+ DLBCL
Ki67	Variable staining	Confirms high proliferation rate
CD30	10–20%	Common in anaplastic variant, prognostic relevance, therapeutic implications
Cyclin D1	0%	Excludes blastic mantle cell lymphoma

Recommendations

- Excisional lymph node biopsy is recommended for diagnosis, although core biopsy may be adequate in many cases. Fine needle aspiration is inadequate. (I, A)
- All biopsies should be reviewed by a histopathologist with lymphoma expertise (I, A)
- FISH for *MYC* +/− *BCL2 and BCL6* should ideally be performed on all cases, with rearrangement partner established where feasible (II, A)

Staging and initial work-up

Thorough and expedient work-up of DLBCL is critical. Recommended work-up is in Table 2. Patients with highly symptomatic, bulky or clinically aggressive disease may require inpatient work-up to expedite delivery of chemotherapy. Pre-phase corticosteroids may also be required.

Recommendations

- Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) combined with computed tomography (CT) is the staging modality of choice, with stage assigned by the Lugano classification (Table 3) (I, A)[9]
- All cases should be discussed in a lymphoma multidisciplinary meeting (IV, A)
- Magnetic resonance imaging brain and spine and cerebrospinal fluid analysis is recommended for patients at high risk of CNS involvement (e.g. CNS-IPI ≥ 4, multiple extranodal sites; see CNS prophylaxis section) (III-2, A)[10]
- FDG-PET is adequate staging for concordant marrow involvement, although biopsy may identify discordant low-grade lymphoma and can be considered when this will alter management (I, B)[11]
- Counselling regarding contraception, menstrual management, pregnancy screening and fertility preservation should occur prior to administration of chemotherapy where clinically appropriate (IV, A)

Table 2 Work-up and staging

History	Presence of 'B' symptoms ECOG performance status History of immunosuppression Prior malignancy and chemotherapy (especially anthracycline) exposure
Physical examination	Involved nodal and extranodal sites Testicular examination in men
Blood tests [9,138–140]	FBE with film and flow cytometry to exclude circulating lymphoma Standard biochemistry (including calcium and phosphate), liver function, LDH, uric acid, beta-2 microglobulin, serum protein electrophoresis. Serology for HIV, Hepatitis B and C, EBV (plus PCR in cases of suspected immunosuppression-related DLBCL) Pregnancy test in women of child-bearing potential.
Cardiac assessment	Transthoracic echocardiogram or gated heart pool scan for assessment of left ventricular ejection fraction
Imaging[9,138]	FDG-PET + CT (staged by Lugano classification, Table 3) Contrast-enhanced CT in addition to FDG-PET in selected cases
CNS assessment[10]	Magnetic resonance imaging brain +/− spine and lumbar puncture for CSF cytology and flow cytometry in patients at risk of secondary CNS disease sufficient to justify prophylaxis (see CNS prophylaxis section)
Bone marrow aspirate and trephine[11]	FDG-PET has largely obviated the need for marrow assessment in DLBCL. It is still recommended in selected cases where the discovery of discordant marrow involvement would alter management

CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; ECOG, Eastern Cooperative Oncology Group; FBE, full blood examination; HIV, human immunodeficiency virus; FDG-PET, 18F-fluorodeoxyglucose—positron emission tomography; LDH, lactate dehydrogenase; PCR, polymerase chain reaction.

Table 3 Lugano classification of lymphoma staging

Stage	Involvement	Extranodal status
Stage I (limited)	One node or group of adjacent nodes	Single extranodal lesion without nodal involvement
Stage II (limited)	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal with limited contiguous extranodal involvement
Stage II bulky	As above with one lesion ≥7.5 cm	
Stage III	Nodal disease above and below the diaphragm with spleen involvement	Not applicable
Stage IV	Additional non-contiguous extranodal involvement	Not applicable

Prognostic factors

IPI and clinical factors

Several prognostic tools discriminate DLBCL risk groups. The original International Prognostic Index (IPI) and the age-adjusted IPI (aaIPI)[12] were first described in the pre-rituximab era, but the same factors maintain prognostic significance in the rituximab era (revised-IPI).[13] The National Comprehensive Cancer Network (NCCN)-IPI incorporates specific extranodal involvement, LDH and age to better stratify DLBCL risk when treated with Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) (Table 4).[14]

Tumour bulk (≥7.5 cm in maximal diameter) has been associated with poor prognosis in R-CHOP-treated patients.[15] Bone marrow, testicular, adrenal, renal, uterine involvement, primary breast DLBCL and high IPI are independently associated with higher CNS relapse risk.[16]

Molecular biology and biomarkers

Numerous pathobiological factors have been identified that add prognostic value to the IPI. The following have the most comprehensive data.

Cell of origin

GEP identifies least three distinct molecular subtypes of DLBCL, arising at the various stages of differentiation. These are the germinal centre B-cell like (GCB), activated B-cell like (ABC) and an unclassifiable group.[17] When tested via GEP there is a clear and reproducible negative prognostic impact of the ABC subtype.[17,18]

The reported impact of IHC-assigned cell of origin (COO) has been inconsistent, although probably retains some prognostic value.[19] The Hans algorithm (Fig. 1) is most frequently used due to simplicity, availability and relative concordance with GEP.[20]

Protein expression

The dual expression (DE) of MYC (≥40%) and BCL2 (≥50%) proteins by IHC has shown prognostic significance independent of the IPI and COO; indeed, it has been suggested that DE-DLBCL accounts for the poor outcomes of ABC-type DLBCL where DE is more common.[17,21,22]

Chromosomal translocation

Single translocations involving solely *MYC, BCL2* or *BCL6* have not been consistently associated with prognosis. FISH studies showing *MYC* and *BCL2* and/or *BCL6* rearrangements define the entity HGBL-DH or HGBL-TH in the World Health Organization 2016 classification and

Table 4 International prognostic index and subsequent variations

Prognostic factor	IPI	aaIPI (≤60 years)	aaIPI (≤60 years)	R-IPI	NCCN-IPI
Age (years)					
41–60	0	0	0	0	1
61–75	1	N/A	N/A	1	2
>75	1	N/A	N/A	1	3
Normalised serum LDH					
>1 to ≤3× ULN	1	1	1	1	1
>3× ULN	1	1	1	1	2
ECOG performance status ≥2	1	1	1	1	1
Stage III or IV	1	1	1	1	1
Specific extranodal sites: bone marrow, CNS, liver/GI tract or lung	0	0	0	0	1
Any extranodal disease (>1 total)	1	0	0	1	0
Risk group	Low: 0–1 (5-year OS 73%)	Low: 0 (5-year OS 83%)	Low: 0 (5-year OS 83%)	Very good: 0 (4-year OS 94%)	Low: 0–1 (5-year OS 96%)
	Low-intermediate: 2 (5-year OS 51%)	Low-intermediate: 1 (5-year OS 69%)	Low-intermediate: 1 (5-year OS 69%)	Good: 1–2 (4-year OS 79%)	Low-intermediate: 2–3 (5-year OS 82%)
	High-intermediate: 3 (5-year OS 43%)	High-intermediate: 2 (5-year OS 46%)	High-intermediate: 2 (5-year OS 46%)	Poor: 3–5 (4-year OS 55%)	High-intermediate: 4–5 (5-year OS 64%)
	High: 4–5 (5-year OS 26%)	High: 3 (5-year OS 32%)	High: 3 (5-year OS 32%)		High: ≥6 (5-year OS 33%)

aaIPI, age-adjusted IPI; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NCCN, National Comprehensive Cancer Network; OS, overall survival; R-IPI, Revised-IPI; ULN, upper limit of normal.

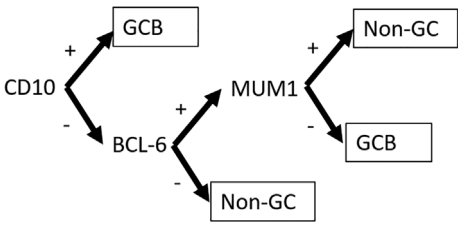

Figure 1 Hans classification of diffuse large B-cell lymphoma (DLBCL) phenotype. Confirmation of the molecular classification of DLBCL by immunohistochemistry using a tissue microarray. GCB, germinal centre DLBCL; non-GC, non-germinal centre DLBCL.

are generally associated with a poor prognosis.[4] However, the original retrospective studies suffered from selection bias, with unselected registry-based testing showing a more favourable outlook (5-year progression-free survival (PFS) ~58%, 5-year overall survival (OS) ~60%). The *MYC* translocation partner also appears of prognostic relevance, with translocations to an immunoglobulin gene (Ig) conferring the highest risk and a non-Ig partner conferring no additional risk; thus, assessment of the break partner should be performed if feasible.[23]

Figure 2 demonstrates the relationship between COO, antigen overexpression and rearrangement of MYC and BCL2.[24]

Interim PET

Interim FDG-PET (iPET) has been assessed for its prognostic benefit and subsequent therapeutic implications. Although data are conflicting, most recent studies demonstrate a clear and independent association between iPET positivity and inferior outcomes.[25–29] The most robust prognostic measure appears to be the change in maximum standard uptake value after four cycles of R-CHOP; Deauville scores of 5 at this time point also predict refractory disease.[30,31] FDG-PET following two cycles also has prognostic importance and can predict early progression.[32] No randomised study has demonstrated a benefit of dose escalation based on iPET and thus no recommendation for change in therapy based on iPET can be made for routine clinical practice.[32,33] There is insufficient evidence to support de-escalation of therapy for early responders.

Recommendations

- The IPI should be recorded in all patients with DLBCL and the NCCN-IPI provides the best discrimination between prognostic groups (I, A)[34]
- COO should be determined in all cases of DLBCL and with specification of the method used (I, A)[4]
- All patients should have IHC for MYC and BCL2 (I, B)

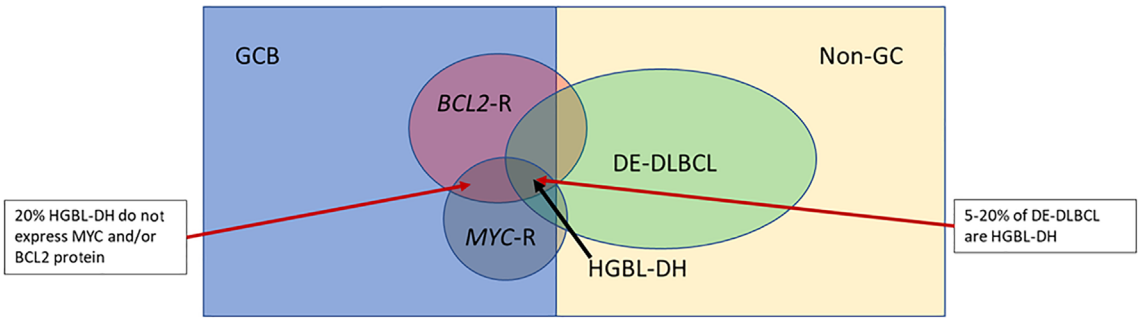

Figure 2 Relationship between cell of origin, antigen expression and chromosomal rearrangements. GCB, germinal centre diffuse large B-cell lymphoma (DLBCL); HGBL-DH, high-grade B-cell lymphoma with rearrangements of MYC and/or BCL2 and BCL6; non-GC, non-germinal centre DLBCL.

- Interim FDG-PET adds prognostic value and may be performed following two or four cycles of R-CHOP (I, C)
- Primary therapy should be completed provided there has been at least a partial response on interim FDG-PET (I, B)

Treatment

Primary chemoimmunotherapy

Standard treatment with chemoimmunotherapy results in OS rates of approximately 70%, 60% and 45% at 3, 5 and 10 years respectively.[34]

All patients should receive rituximab in combination with chemotherapy given its addition confers a significant survival advantage with little additional toxicity.[35–39] The combination of rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy is the standard regimen for most patients with DLBCL due to efficacy and tolerability.[40–44]

In unselected DLBCL, R-CHOP given every 21 days (R-CHOP21) showed equivalent efficacy with improved tolerability compared with a 14-day schedule (R-CHOP14) and remains the recommended front-line treatment.[45–47] For patients with advanced-stage disease, six cycles provide similar efficacy to eight cycles.[39,48] There is no role for consolidation autologous stem cell transplantation (autoHCT) or maintenance therapy post R-CHOP for patients achieving complete metabolic response (CMR) due to absence of overall survival advantage.[49–53]

Recommendations

- Six cycles of R-CHOP21 is recommended for first-line advanced-stage DLBCL (I, A)
- Timely, full-dose therapy should be delivered in patients <80 years of age where organ function and toxicity allow (III-1, A)[48]
- AutoHCT or maintenance therapy should not be used to consolidate DLBCL in complete metabolic remission following R-CHOP (I, A)
- For patients with limited stage, non-bulky (<7.5 cm), IPI 0 disease four cycles of R-CHOP21 followed by two cycles of rituximab monotherapy is equivalent to six cycles (II, A)

Consolidation radiation therapy

Radiation therapy (RT) is an effective locoregional consolidative therapy for DLBCL. Consolidation RT is most useful where risk of local relapse is the dominant site of failure, even after effective systemic therapy.

Primary indications for RT in first-line management of nodal DLBCL include: (i) chemotherapy minimisation strategy in non-bulky limited-stage disease;[54,55] (ii) to consolidate sites at high risk of local relapse (e.g. bulky disease ≥7.5 cm);[56,57] and (iii) to convert partial metabolic responses to complete response after initial chemoimmunotherapy.[58] Indications for RT in extra-nodal DLBCL sites are presented in other international guidelines.[59]

In general, doses of 30–36 Gy are recommended to consolidate sites in CMR, delivered in 1.5–2 Gy per fraction.[60,61] Doses of 36–50 Gy may be required for FDG-PET-avid residual masses.[61]

Limited stage disease (non-bulky)

Conventional treatment approaches for non-bulky, limited stage disease include either: (i) full course chemoimmunotherapy (six cycles of R-CHOP);[56,62] or (ii) abbreviated chemoimmunotherapy (3–4 cycles of R-CHOP) with consolidation involved site RT (ISRT).[54,63,64] Where tolerated, full-course chemoimmunotherapy is

the preferred strategy for patients with higher risk disease, based on the continued pattern of late relapses observed following abbreviated systemic therapy in patients with stage-adjusted IPI ≥1.[63] However, for patients who may not tolerate full course chemoimmunotherapy, abbreviated chemoimmunotherapy and 30 Gy ISRT offers equivalent survival outcomes[63] with reduced chemotoxicity and acceptable radiation-induced toxicity profile.[55,60,64,65]

For young (age ≤60 years) low-risk patients (aaIPI 0), four cycles of R-CHOP21 and two additional doses of rituximab without RT is non-inferior to six cycles of R-CHOP, with expected reduction in toxicity.[66] For patients aged >60 years with no other IPI risk factors, abbreviated chemotherapy without radiotherapy may also be a reasonable option in patients with a negative iPET, but this approach has not been subjected to a randomised study.[67] This approach is probably not suitable for patients with additional IPI risk factors where the preferred approach is six cycles of R-CHOP.[68]

Bulk

Several studies in the pre-FDG-PET era have demonstrated the benefit of consolidation RT to bulky or extranodal sites.[56,57] Omission of RT to original sites of bulk that achieve CMR by end of chemoimmunotherapy but have an incomplete CT response remains an area of controversy; the results of PET-adapted randomised studies are awaited (e.g. OPTIMAL>60, NCT01478542). Patients with bulky disease should not have systemic therapy abbreviated.

Recommendations

- ISRT is recommended over involved field RT due to equivalent efficacy and lower toxicity (I, A)[64]
- For patients with limited stage disease and stage-adjusted IPI ≥ 1, ISRT should be considered if it is necessary to abbreviate chemoimmunotherapy, for example for toxicity (II-B), although the preferred strategy remains six cycles of R-CHOP[54,63,69]
- ISRT remains standard of care for original sites of bulk (≥7.5 cm) with incomplete CT resolution following R-CHOP (II,B), although omission of ISRT in PET-negative patients may be reasonable if toxicity is prohibitive (III-2,B)[70]
- ISRT is recommended to sites of incomplete metabolic response on FDG-PET unless other salvage is planned and if the disease is encompassable (III-2, A)
- For patients aged ≤60 years with aaIPI = 0, low-bulk, limited stage disease with CMR at chemoimmunotherapy completion, radiotherapy may be omitted (I,A).[66] A similar approach in patients aged >60 years may be considered after a discussion of risks and benefits (III-2, C)[67]

Poor risk disease

No randomised trial data supports using intensive regimens over R-CHOP21. However, such studies have not been powered to address patients with high clinical risk scores (e.g. aaIPI 2–3), so the question of whether intensified regimens improve outcomes for patients with both advanced-stage and high IPI disease has not been definitively answered.[45,46,71] R-CHOEP14 (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) has shown relatively favourable outcomes in younger, high-risk patients but has not been compared with R-CHOP21 directly.[72]

The poor outcome of advanced-stage HGBL-DH, frequent association with other high-risk clinical factors, and poor chance of salvage on treatment failure has led to the widespread but speculative adoption of more intensive chemotherapy regimens such as R-DA-EPOCH and R-CHOEP14 with or without high-dose autoHCT consolidation in first remission. Evidence for such approaches is limited to retrospective studies, which suggest a higher CR rate following intensified induction, and which show no clear advantage to autoHCT in first complete response.[73,74]

Recommendations

- Patients with high biological risk should be enrolled in clinical trials where possible
- No alteration of treatment strategy is recommended based on COO, DE or lone *MYC* rearrangement (I, A)
- Intensification to R-DA-EPOCH or R-CHOEP14 in younger fit patients with aaIPI 2–3 and in HGBL-DH may be justified in selected cases following discussion about the risks and benefits (III-2, C)

Management of elderly patients with DLBCL

The potential for cure is reduced in the elderly due to increased likelihood of aggressive disease biology, medical comorbidities, functional decline and reduced tolerance of intensive chemotherapy.[75,76] There is no universally accepted definition of 'elderly' DLBCL patients in the literature. Until recently elderly patients with DLBCL were under-represented in clinical trials, thus the optimal treatment for these patients remains unclear.

For fit older patients aged <80 years, six cycles of R-CHOP21 is suggested with supportive measures as listed below, and geriatric assessment tools may assist in determining fitness.[77] For patients aged >80 years or those unfit for full dose R-CHOP21, R-mini-CHOP is a

reasonable option with a reported 2-year OS and PFS of 59% and 47% respectively.[78] For unfit or frail patients regimens such as R-GCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone),[79] R-mini-CEOP (with epirubicin)[80] or R-CEEP (rituximab, cyclophosphamide, epirubicin, etoposide, prednisolone)[81] can be considered. R-CEOP (with etoposide) is an option for patients ineligible for an anthracycline.[82]

Recommendations

- The use of a geriatric assessment tool is recommended to guide treatment choice in elderly DLBCL patients (IV, C)
- Pre-phase prednisone is recommended in elderly patients (III-2, B)[83]
- Prophylactic Granulocyte colony stimulating factor is recommended for all cycles of therapy (III, B)[84]
- Vitamin D supplementation should be considered in deficient patients (IV, C)[85–87]
- For fit older patients, six cycles of R-CHOP21 is recommended with the above supportive measures (I, A)[77]
- For patients aged >80 years or those unfit for R-CHOP21, R-mini-CHOP is a reasonable option (III-2, B)
- Abbreviated therapy (3–4 cycles of R-CHOP) plus ISRT can be considered in elderly patients with limited stage, non-bulky disease (II-B)

Synchronous CNS/systemic disease

Patients presenting with synchronous CNS involvement at first presentation of systemic DLBCL have a poor prognosis driven largely by the CNS disease.[10] Some data support the use of AutoHCT in first complete remission, although the benefit is unclear if primary induction therapy includes high-dose methotrexate and cytarabine.[10,88] Recently published prospective trials taking an intensive induction approach with or without consolidative AutoSCT had relatively favourable outcomes in this group.[89,90] Intrathecal therapy can be added in those with leptomeningeal disease, and consolidation with radiotherapy and autoHCT at the discretion of the treating clinician is based upon disease response and patient factors.

Recommendations

- Patients with synchronous CNS and systemic DLBCL at diagnosis should receive a combination chemotherapy regimen that includes high-dose intravenous methotrexate and cytarabine as well as standard chemo-immunotherapy, which is usually achieved with alternating treatment cycles. Consideration may be given to consolidation AutoHCT and RT (III-2, B)

CNS prophylaxis

Unselected DLBCL carries ~5% risk of CNS relapse and patients at high risk should be identified at diagnosis.[91] The most commonly used clinical risk score is the CNS-IPI, which adds renal and adrenal involvement to the standard IPI factors to identify patients at high risk of CNS relapse.[92] However, a high-risk score (≥4) only identifies 55% of patients who will experience CNS relapse and we therefore also consider patients with more than two extranodal sites as high risk.[93] Additional specific extranodal DLBCL sites appear to carry an independent CNS risk including testis, uterus and breast.[94–96] Certain biological features also appear to increase the risk of CNS presentations, including ABC subtype (particularly C5/MCD types),[97–99] DE-DLBCL and possibly HGBL-DH.[74,100]

The role of CNS prophylaxis is controversial with conflicting data and forthcoming randomised clinical trials are unlikely due to the relative infrequency of events. Recent retrospective analyses casts doubt on the benefit of intravenous methotrexate prophylaxis, although were likely underpowered.[101] Intensive systemic regimens with inbuilt CNS-penetrating agents and the administration of high-dose intravenous methotrexate appear to lower the risk of CNS progression; the latter with less associated toxicity.[102–104]

Recommendations

- Intrathecal methotrexate prophylaxis is not recommended unless systemic prophylaxis is not deliverable (III-2, B)[103,105]
- Two to three cycles of high-dose intravenous methotrexate (e.g. 3 g/m^2) in addition to R-CHOP21 is reasonable in patients with high CNS-IPI and those with multiple or specific extranodal sites (III-2, C)[103,104]
- CNS prophylaxis in patients with high biological risk DLBCL but low- or intermediate-risk CNS-IPI scores should be discussed on a case-by-case basis
- CNS-penetrant therapy may be delivered at the completion of or intercalated with R-CHOP, although an intercalated approach may increase toxicity and compromise R-CHOP delivery[106]

Response assessment and follow up

Following completion of induction chemo-immunotherapy, patients should be re-evaluated to confirm disease response. The end of treatment (EOT) imaging modality of choice is FDG-PET/CT, which may also be helpful in guiding RT dose prescription and planning.[107]

On achieving CMR, conventional practice is for 5 years of follow up for monitoring of complications of therapy and disease relapse.[108] Surveillance imaging for relapse detection is low yield and confers no survival advantage compared with clinically detected relapse. Therefore, the present surveillance strategy centres on clinical and laboratory findings, with imaging indicated only when there is clinical suspicion of relapse. Interval FDG-PET may be used in cases where the EOT FDG-PET is equivocal.

Recommendations

- EOT FDG-PET/CT should be performed at least 3 weeks, and preferably 6–8 weeks after completion of chemoimmunotherapy, and 8–12 weeks after the completion of RT[107]
- We recommend defining complete metabolic remission in accordance with the Lugano classification (I, A)[9]
- Imaging for the detection of relapse should be performed due to clinical suspicion rather than surveillance (III-2, B)[109,110]

Relapsed/refractory DLBCL: transplant-eligible patients

In transplant-eligible patients experiencing first relapse/progression, salvage chemoimmunotherapy followed by autoHCT provides a survival benefit over salvage therapy alone.[111] Disease response as determined by FDG-PET is the most critical factor in proceeding to autoHCT, and depth of response pre-transplant correlates with post-transplant outcomes.[112] There is no routine role for allogeneic transplantation in second complete remission.[113]

The commonly used salvage and autoHCT conditioning regimens are summarised in Table 5, although there are currently insufficient data to recommend one over another. The only two randomised studies failed to show a difference in response or survival for R-ICE vs R-DHAP and R-DHAP vs R-GDP, respectively, although R-DHAP appears more toxic.[114,115] Additionally, ofatumumab offered no benefit over Rituximab with a DHAP backbone.[112] There is no benefit to rituximab maintenance following autoHCT.[116]

Radiotherapy before or after autoHCT to consolidate responses should be decided on a case-by-case basis, typically where all sites of disease can be addressed within a radiation field. Guidelines were recently published by ILROG.[117]

Myeloablative conditioning regimens for autologous HCT have not been directly compared in prospective trials. BEAM is the most commonly used regimen.[118]

Recommendations

- In patients experiencing first relapse/progression who are eligible for high-dose chemotherapy with autoHCT, we recommend salvage chemoimmunotherapy followed by autoHCT (I, A)
- Sensitivity to salvage chemoimmunotherapy as determined by FDG-PET is a prerequisite to proceeding to autoHCT due to high failure rates with chemoresistance (III-2, A)[119–123]
- Consideration should be given to alternative or additional salvage strategies for responding patients failing to achieve CR by FDG-PET prior to autoSCT. Options including proceeding to AutoSCT, radiotherapy, CAR-T

Table 5 Lymphoma salvage regimens and autologous transplant regimens

A. Salvage regimens

Regimen	Overall response rate	CR rate	% Received autoHCT
R-GDP[114]	45%	13.5%	51%
R-ICE[115]	63%	36%	51%
R-DHAP[114,115]	44–64%	14–40%	49–55%
R-ESHAP[141]	67%	37%	62%

B. AutoHCT conditioning regimens

Regimen	PFS	OS
BEAM[118]	47% at 3 years	58% at 3 years
LACE[142]	42% at 5 years	47% at 5 years
BuMel[143]	64% at 2 years	67% at 2 years
Stanford BCNU[118]	39% at 3 years	43% at 3 years

AutoHCT, autologous haemopoietic cell transplant; BEAM, carmustine, etoposide, cytarabine, melphalan; BuMel, busulphan, melphalan; BCNU, carmustine; LACE, lomustine, cytarabine, cyclophosphamide, etoposide; OS, overall survival; PFS, progression-free survival; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-ESHAP, rituximab, etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP, rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE, rituximab, ifosphamide, carboplatin, etoposide.

cells and clinical trial should be decided on a case-by-case basis (III-2, C)

Relapsed/refractory DLBCL: transplant-ineligible patients

The management of relapsed/refractory (R/R) DLBCL in transplant-ineligible patients is often non-curative, although a proportion of patients with refractory disease encompassable in a single RT field may be cured by this approach.[124] For the remainder, there is no standard approach, and thus we recommend early consideration of active clinical trials where available. Chimeric antigen receptor T-cell therapy (CAR-T) beyond second-line treatment can offer durable remissions and probably cure in 30–40% of treated patients. CAR-T are approved in Australia in patients who have relapsed or who are refractory to at least two lines of systemic treatment, and who have relapsed or are ineligible for a transplant. However, the complexity of the procedure precludes its use in many patients, especially those with refractory lymphoma or medical comorbidities.[125,126] While an in-depth discussion of this topic falls outside the scope of this manuscript, it is recommended that an early discussion with a CAR-T centre should be considered where clinically appropriate.

For many patients, a potentially curative option is unavailable, and the goal of therapy is disease control and quality of life, thus more intensive salvage regimens are usually inappropriate. Gemcitabine-based regimens offer a reasonable combination of efficacy and tolerability.[114,127–131] Novel agents such as polatuzumab-vedotin with bendamustine and lenalidomide may provide additional options in selected cases, pending regulatory approval/reimbursement in Australia.[132,133] Radiotherapy and high-dose corticosteroid may provide symptom palliation. Higher dose RT may achieve durable remissions in the uncommon circumstance of localised R/R DLBCL.[59]

Recommendations

- We recommend enrolment in clinical trials as the first option where available for transplant-ineligible R/R DLBCL patients
- CAR-T therapy provides a potentially curative option for some patients and early discussion with a CAR-T centre is recommended if this approach is considered
- RT should be considered for patients with limited-stage relapse

Future directions and research priorities

An immense amount of research has been conducted in DLBCL since the introduction of rituximab without significant improvement in outcomes. Several studies have investigated the addition of novel agents to patients with poor biological risk tumours without a survival advantage.[134–136] As our understanding of the genetic and functional drivers of DLBCL increases, clinical trial design needs to evolve to address not only those patients with poor prognostic disease, but rational drug combinations that target pathogenic mechanisms.

Antibody–drug conjugates such as polatuzumab-vedotin clearly have activity in relapsed and refractory disease and are currently being investigated in the up-front setting (NCT03274492). While CAR-T therapy is approved in the third-line setting, ongoing trials are actively exploring their role in high-risk first relapse in the transplant-eligible population. Bispecific T-cell engaging antibodies also show significant promise in chemorefractory disease.

Improving access to treatment for certain subgroups such those from regional and remote areas remains a challenge and the use of telehealth and teletrials technology may improve the disparate outcomes for these patients.

Methodology

These consensus practice statements were developed in accordance with the ALA policy for Consensus Practice Statement development. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the NHMRC evidence hierarchy shown in Tables S1 and S2.[137] Statements without grading were considered justified standard clinical practice by the experts and the ALA members. The manuscript has been subjected to an anonymous peer-review process.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1. Levels of evidence.
Table S2. Grades of recommendations.